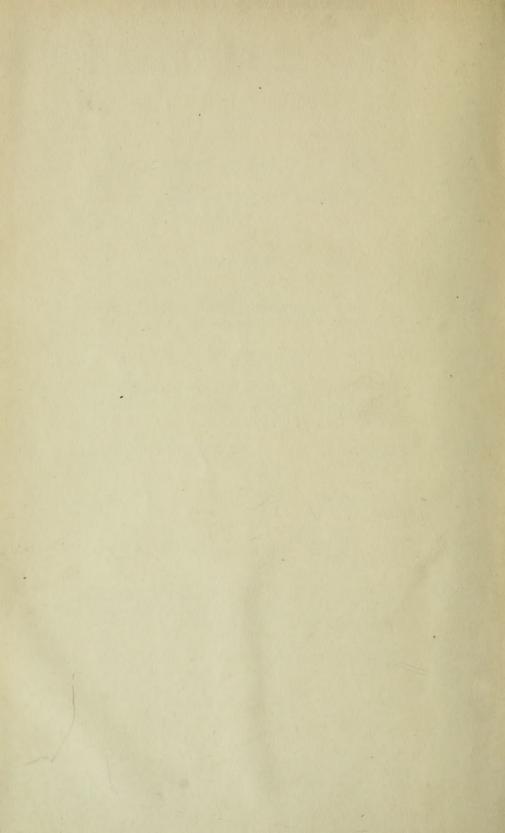MEDICAL RESEARCH COUNCIL.

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MEDICAL RESEARCH COUNCIL

no. 60

The Use of Death-rates as a Measure of Hygienic Conditions

By John Brownlee, M.D., D.Sc.

Medical Research Council.

THE USE OF DEATH-RATES AS A MEASURE OF HYGIENIC CONDITIONS

BY

JOHN BROWNLEE, M.D., D.Sc., Director of Statistics, Medical Research Council.

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PART I

PART II

I. Introduction.

' Those to whom the King had entrusted me observing how ill I was clad ordered a tailor to come next morning and take measure for a suit of clothes. This operator did his office after a different manner from those of his trade in Europe. He first took my altitude by a quadrant and then with rule and compasses described the dimensions and outlines of my whole body, all which he entered upon paper : and in six days brought my clothes, very ill made, and quite out of shape by happening to mistake a figure in the calculation. But my comfort was, that I observed such accidents very frequent and little regarded.'

In the following pages it is proposed to criticize the methods that have been and may be employed to draw conclusions from the manner in which death-rates experienced among those who live in different environments or those who work in different industries may vary, and, if possible to discover what are the canons of just inference from such data as are at our disposal. This seems to be specially important at the present time, a time when administrative measures competent to ameliorate unfavourable social conditions are expected in reply to instant demand. To determine how to act best requires exact knowledge, a knowledge not to be attained without

a full appreciation of the error which may arise in making deductions from the different measures in which the data are recorded.

The data which are at our disposal to determine many of these questions unfortunately relate only to deaths and not to incapacity. In the best class of such evidence the actual death-rates can be calculated for deaths against known populations. In another class of statistics, however, the deaths alone are known and the only comparison possible is between the number of deaths from any cause and the total number of deaths from all causes. These two categories obey different laws and require quite different methods of statistical treatment. It is commonly believed that deductions based upon data of the first kind are unassailable while deductions based upon data of the second must be regarded with distrust. The problem, however, is not nearly so simple as this. In both cases there are many fallacies which must be avoided. These will be discussed in the appropriate place. For the present it is sufficient to give two examples.

The mean age at which deaths from measles occur in towns is considerably lower than that in the country. As nearly every one exposed to measles develops the disease an adequate explanation is at once suggested. The phenomenon is due to the fact that epidemics occur at shorter intervals in the towns than in the country, and in consequence there is on the average a larger susceptible population at higher ages in the latter. On the other hand a disease such as cancer, which many hold to be degenerative and not parasitic, has a similar difference in its age incidence, deaths in towns occurring on the average at an earlier age than deaths in the rural districts. An explanation of the difference cannot in this case be sought directly from the side of infection. The difference will be shown later to be quite independent of this theory of causation.

Thus even when the numbers of deaths and of the corresponding populations at each age period are known it is often difficult to determine the significance of the figures. When the number of deaths alone is known the matter is still more complex. In both cases it is nearly true to say that each disease requires special consideration, but though this may be or may not be required in the first category, it is always required in the second. It is to examine how far the different measures of the death-rates are measures of comparison, and to discuss the range in which each of these measures is of practical importance, that the following pages have been put together.

The method of presenting the subject-matter adopted is in the first place to discuss all the essential facts as clearly as possible in the text, adding at the same time a series of tables and diagrams. The description of the important technical methods is not placed in the text but in the subsidiary explanation attached to these tables and diagrams. Purely mathematical processes are placed in Part II. It is hoped that this arrangement will enable each reader to find what he wants. I do not know whether such a subdivision of the discussion will be approved, but at the present moment with the great difference of mathematical attainment in the health services it seems necessary to grade the discussion of any technical matter on a series of levels, (1) for the generally informed

person, (2) for the executive official such as the medical officer of
health, (3) for the statistician. To write for each severally is impos-
sible. It is further undesirable as the knowledge of most persons
is not limited to one range. The test of the art of any author at
present is therefore his capacity to write for all three at once.

In certain places where a passage of my own already published
seems to describe some phenomenon more concisely than is in my
power to improve, this passage has been transferred to the present
text without the addition of marks of quotation. After all, it cannot
reasonably be expected that a purple patch can be written more
than once. I have to thank Dr. Major Greenwood for reading the
proof, and also am under great obligation to Sir Alfred Watson and
Mr. A. Henry for the care with which they investigated a number of
special points.

PART I. DEATH-RATES IN GENERAL

II. Crude Death-rates.

The first measure of mortality introduced statistically was the
ratio of the number of deaths in each year to the average number
of persons living during that year. This was commonly expressed
as a fraction. Thus a mortality of $\frac{1}{20}$ signified that out of every
1,000 persons constituting the population 50 died in each year,
while a mortality of $\frac{1}{50}$ signified that out of each 1,000 persons 20
died. This method of describing the mortality by a fraction has
grave inconveniences. It is inverse in character, difficult to print
and to read, while the comparison of the hygiene of one district with
another involves undue mental effort.

At the present moment the death-rate is stated as a proportion of
the number dying per annum to the number living, and is expressed
in units per thousand. Thus, if 33 persons die in each 1,000 of
the population, the death-rate is said to be 33 per 1,000. This
method is direct and much more convenient both from the point of
view of printing and of thinking. It is in addition, in spite of its
drawbacks, which will presently be discussed, a measure which in
general is not far from representing the facts in a manner easily
understood.

When the change took place from the one system to the other
I do not know. The data of Dr. Heysham, 1780–8, on which the
Carlisle Life Table was founded, are expressed in the first method.
In 1829 Dr. Hawkins still employed it in his Goulstonian Lectures
on Medical Statistics. In 1837, however, in Dr. Farr's creative
article on ' Vital Statistics ' in McCulloch's *Statistical Survey of the
British Empire* the new method is employed. As Dr. Farr imme-
diately thereafter became medical adviser to the Registrar-General,
it is no wonder that the method finds its place in the publications
issued by that newly-founded office. The formation of this con-
venient comparative standard must thus, I think, be ascribed to
Dr. Farr. In some important statistical returns, however, such as
those issued by the City Chamberlain in Glasgow, Mr. Watt, both

TABLE I. *Illustrating the proportionate distribution of the population in each age and sex group.*

Age Period	Nine Rural[1] Registration Districts of Yorkshire. 1891-1900.		Doncaster. 1891-1900.		Liverpool Registration District.		Pollokshields.		Health Districts in Glasgow, Springburn. 1890-1903.		Cowcaddens.	
	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.
0–5	5·91	5·89	6·31	6·43	5·41	5·43	2·53	2·67	7·35	7·37	5·62	5·55
5–10	5·92	5·78	5·95	5·98	5·00	5·10	2·82	2·54	6·22	6·21	5·39	5·20
10–15	5·71	5·60	5·47	5·31	4·95	4·98	3·25	3·55	5·23	5·23	5·13	5·28
15–20	5·41	4·90	5·15	4·60	4·77	5·17	3·87	6·56	4·69	4·24	5·01	5·07
20–25	4·06	4·33	4·69	4·32	4·65	5·41	3·74	8·61	4·40	4·38	4·73	4·70
25–35	6·36	7·05	7·93	7·43	8·31	8·54	6·51	12·70	8·96	8·59	8·63	8·12
35–45	5·50	5·68	6·05	5·69	6·73	6·54	5·02	8·44	6·58	5·95	6·40	6·40
45–55	4·46	4·37	4·40	4·16	5·03	4·89	4·90	7·24	4·10	3·79	4·63	4·85
55–65	3·25	3·25	2·79	2·85	2·86	2·94	3·83	4·67	2·15	2·14	2·67	3·08
65–75	2·19	2·18	1·51	1·69	1·19	1·41	2·06	2·88	0·91	1·05	1·07	1·77
75+	0·96	1·04	0·57	0·72	0·25	0·44	0·64	0·97	0·16	0·30	0·25	0·45
Total	49·93	50·07	50·82	49·18	49·15	50·85	39·17	60·83	50·75	49·25	49·53	50·47

[1] Sedbergh, Settle, Great Ouseburn, Patrington, Driffield, Malton, Easingwold, Guisborough, Bedale.

DESCRIPTION OF TABLE I

In this table the variations which may take place from district to district in the relative age and sex constitution of the population is shown. In the first half of the table the figures are given for three districts in the north of England. It will be noted how in the rural districts the proportion of persons at upper ages is very high as compared with what is found in Liverpool, and that in the rural districts the defect of the population is Pollokshields representing the type of residential villa population. In the second half of the table three health districts of Glasgow are compared. One of these the ratio being three females to two males. A great part of this excess occurs between the ages of 15 and 45 years, the ages at which domestic service is most common. The very small proportion of children is also to be noted. The second of the districts is Springburn, a good working-class district. Here we have a large proportion of persons at early adult ages, a large number of children and relatively few persons at the higher ages; the proportion above 75 years for the males and females being respectively 0·16 and 0·30 as against 0·96 and 1·04 in the rural districts of Yorkshire. The third district, Cowcaddens, is a slum. The proportions of the population do not greatly differ from those in Springburn except in the ages of childhood and in old age, there being a defect in the former and an excess in the latter.

methods are employed till the middle forties of last century, and
even the shipping health returns of the Board of Trade employ the
earlier method to the present day.

For its immediate purposes this death-rate, now termed the
crude death-rate, was quite sufficient. Its disadvantages as a measure
appeared later. These disadvantages, now well known to every
schoolboy, as Macaulay would have said, are that from place to place
the population varies in constitution of age and sex. Extending
manufacturing towns such as Doncaster (Table I) are peopled
largely by young married couples, and though the mortality of
infants is very high, yet, as normally the chief number of deaths
takes place at the later ages of life, and as the numbers living at
these ages in a population such as just described are in defect, the
crude death-rate as a measure of the deleterious effects of city life
is unduly small. Rural districts (Table I) show the opposite con-
dition, elderly persons being in great excess. Still more artificially
small death-rates are found in city suburbs where, in addition to
the proportion of children being unfortunately progressively smaller
and smaller, the number of maid-servants at healthy ages of life
employed is in great excess. These if mortally affected as a rule
return home to die. The result of such a concatenation of individuals
is to produce, as not unusual, crude death-rates of 7, 8, or 9 per
thousand. The manner in which the different districts of a town
may vary is shown for Glasgow (Table I). Pollokshields is a resi-
dential district such as has just been referred to, Springburn a good
working-class district, and Cowcaddens a slum.

Whatever error arises in forming crude death-rates when whole
populations are taken into account, it is nothing to what may
arise when individual trades or professions are compared. Of this
an example is given in the accompanying table (Table II), in which

TABLE II. *Showing a comparison between the health of clergymen
and railwaymen, 1900–02.*

		AGE PERIODS.			
		45–55.	55–65.	65 and upwards.	45 and upwards.
Clergymen	Average number living	8,453	6,886	6,310	21,649
	„ „ of deaths	83	161	521	766
	Death-rate per 1,000 .	9·82	23·43	82·62	35·37
Railway engine-drivers, &c.	Average number living	25,858	11,793	4,540	42,191
	„ „ of deaths	345	351	423	1,119
	Death-rate per 1,000 .	13·33	29·79	93·17	26·52

it is shown, comparing mortalities among railwaymen and clergy-
men, that the death-rates at each age period above 45 years are
very much higher among railwaymen than among clergymen.
Yet when the totals at all ages are taken it is found that the death-
rate among clergymen is very much higher than among railwaymen.
This result is obviously due to the fact, that the proportion of
railwaymen living above 65 years is very much smaller than that
of clergymen. The retired engine-driver, if still fit, drifts into some
other employment and disappears from view, while the clergyman

remains longer at duty and even if retired retains his position among the members of his profession.

In this connexion the controversy initiated in the eighties of last century by the late Sir B. W. Richardson may be recalled. He claimed that death-rates should in no district be more than eight per thousand. Such a crude death-rate may exist but it means nothing. If the population were stationary, as will presently be seen, the average life would be 125 years. I do not think the author of this dictum was convinced of his error, and though he be dead he yet speaketh. I have had the greatest difficulty in convincing members of borough councils in England that such death-rates were death-rates that could only be attained if the Creator reconsidered the principles on which he had changed the dust of the earth into our first parent.

III. Standardized Death-rates.

To meet the difficulties inherent in any method which does not correct for age and sex distribution, standardized death-rates were introduced more than forty years ago. Two methods of standardizing, termed respectively the direct and the indirect methods, are in regular employ. Both are apparently due to Dr. Ogle, and were described at first as ' corrected ' death-rates. At the present moment the term in fashion is ' standardized '. The indirect method is first published in the annual summary of the Registrar-General for 1883, in which the death-rates for the twenty-eight great towns of England and Wales are so calculated. Two years later, 1885, the direct method of comparison appears in the decennial supplement relating to the decade 1871–1880.

The direct method, which seems the most natural, is calculated in the following manner. A population arranged in selected age and sex groups, commonly that of the community which comprehends the whole areas to be examined, is taken as a standard population. Thus in correcting the death-rates for the towns or rural districts of England the population of England and Wales in its age and sex constitution has been taken by the Registrar-General as the standard population. Also in the case of London, where comparison is made between the individual boroughs, the population of London as a whole has been chosen by the Medical Officer of Health as a suitable criterion.

The standard population for practical purposes is arranged in groups of five years of age from birth to twenty-five years of age, and thereafter in groups of ten years. Finer divisions fail to increase the accuracy and greatly increase the labour of calculation. The death-rates for the districts examined are calculated for the same selected age-groups and for each sex separately. These death-rates are multiplied into the respective groups in the standard population. The total number of deaths found is that which would occur under the conditions descriptive of the district examined, that is, if the population in the district were distributed in the same age and sex proportion as that of the whole community (Table III (A)).

The differences produced by local variations in the age and sex

of the population described in the discussion just given may be illustrated from the decade 1891–1900. The crude death-rate in Sedburgh in Yorkshire was in this decade 15·35 per thousand, whereas when standardized it was only 12·72. This is the general rule, as in rural districts there is generally a large proportion of persons living at high ages. The opposite condition obtains in towns, for example, in the Manchester Registration District the crude death-rate in the same decade was 26·4 ; standardized it became 28·3.

The indirect method of calculating a standard death-rate depends on the death-rates in the standard population for each age and sex group (Table III (B)). These rates are multiplied into the corresponding age and sex population groups of the district in which the health conditions are to be investigated. When the calculations have been made a death-rate is found equivalent to that which would obtain if the distribution of death-rates at each age group were the same as that in the standard population. The ratio to this death-rate of the death-rate in the population chosen as a standard will in some cases be greater and in some cases be less than unity. The crude death-rate of the district examined must be multiplied by this ratio. The number thus obtained is the standardized death-rate corrected in the manner described as ' indirect '.

TABLE III. *Illustrating the method of standardizing death-rates by (a) the direct, (b) the indirect method. The example chosen refers to the registration district of Liverpool, 1891–1900, and to nine rural registration districts of Yorkshire, 1891–1900. (Males.)*

(A)

Age Period.	Number of males in standard population.	Death-rates among males in Liverpool.	Number of deaths obtained.	Death-rates among males in the nine rural districts of Yorkshire.	Number of deaths obtained.
0–5	59,052	121·49	7,174	42·71	2,522
5–10	56,000	9·42	528	3·21	180
10–15	53,521	4·64	248	1·97	105
15–20	49,986	7·43	371	2·99	149
20–25	44,106	9·78	431	3·89	172
25–35	74,159	16·63	1,233	4·69	348
35–45	57,412	28·89	1,659	7·04	404
45–55	41,980	44·95	1,887	11·17	469
55–65	27,212	71·00	1,932	22·55	614
65–75	15,026	116·52	1,751	58·32	876
75+	5,603	199·47	1,118	154·09	863
Total	484,057		18,332		6,702

Standardized death-rate
$$= \frac{18,332}{484,057} \times 1,000 = 37\cdot87$$
as against a crude death-rate of 35·77.

Standardized death-rate
$$= \frac{6,702}{484,057} \times 1,000 = 13\cdot85$$
as against a crude death-rate of 15·68.

DESCRIPTION OF TABLE III (A)

In this table the method of formation of a standard death-rate is shown. In the first column the average population of all England, 1891–1900, is given for each age period. In the second column the death-rates in Liverpool at the same ages are shown. The third column is obtained by multiplying the figures in the first two columns together. Thus the population between the ages of 0–5 years, 59,052, with a death-

rate of 121·49 per thousand gives in each year 7,174 deaths. In the same way 56,000 persons living between 5–10 years with a death-rate of 9·42 provide 528 deaths, and so on for each age. The figures thus obtained are summed and the sum divided by the total number in the standard population. In this way a standardized death-rate of 37·87 is obtained against a crude death-rate of 35·77. A second example is given for the rural districts of Yorkshire in columns four and five. In this case a standardized death-rate of 13·85 is found against a crude death-rate of 15·68.

(B)

Age Period.	Death-rates among males in standard population.	Male population in Liverpool.	Number of deaths expected.	Male population in the nine rural districts of Yorkshire.	Number of deaths expected.
0–5	62·71	8,261	518	8,049	505
5–10	4·31	7,640	33	8,063	35
10–15	2·45	7,550	18	7,778	19
15–20	3·79	7,278	28	7,366	28
20–25	5·06	7,105	36	5,528	28
25–35	6·76	12,683	86	8,938	60
35–45	11·50	10,265	118	7,496	86
45–55	18·95	7,676	145	6,072	115
55–65	34·95	4,372	153	4,434	155
65–75	70·39	1,810	127	2,987	210
75+	160·09	380	61	1,307	209
Total		75,020	1,323	68,018	1,450

Death-rate = 19·32

Death-rate found in Liverpool $= \dfrac{1,323}{75,020} \times 1,000 = 17 \cdot 64$

Correcting factor $= \dfrac{19 \cdot 32}{17 \cdot 64} = 1 \cdot 095$

Standardized death-rate
= Crude death-rate × 1·095
= 35·77 × 1·095 = 39·18

Death-rate found $= \dfrac{1,450}{68,018} \times 1,000 = 21 \cdot 33$

Correcting factor $= \dfrac{19 \cdot 32}{21 \cdot 33} = \cdot 9058$

Standardized death-rate
= 15·68 × ·9058 = 14·20

TABLE III (B)

The indirect method of standardizing the death-rate is shown. In the first column the death-rates at each age group for England as a whole are given, and in the second column the numbers living at each age period in Liverpool. These two columns are multiplied together severally as in the previous example and the number of deaths at each age that would occur if the population were as given in column two and the death-rate as in column one are shown in column three. When these deaths are summed and divided by the total population a death-rate of 17·64 is obtained. This would be the death-rate in Liverpool with its age constitution of population if the same death-rates held as are found for the country as a whole. The constitution of the population of Liverpool thus gives a death-rate of 17·64 as compared with that in England as a whole, which is 19·32. To obtain the standardized death-rate, the crude death-rate as found in Liverpool is thus multiplied by the factor obtained by dividing 19·32 by 17·64, or 1·095. The result is to raise the crude death-rate of Liverpool from 35·77 to 39·18. The same process is also shown for the rural districts of Yorkshire.

A comparison of crude death-rates for different conditions of life and of death-rates standardized by the two methods is given in the accompanying table (Table IV) taken from the report by Dr. Stevenson for the year 1911. It will be noted that though the difference between the crude and the standardized death-rates may be fairly large the difference between the two standardized death-rates is very small.

When, however, smaller districts are considered there may not be the same correspondence. In Table III, in which the death-rates of nine rural districts in Yorkshire and the registration district of

Liverpool are compared, the correspondence, though close, differs in the first case by 1·31 per 1,000 and in the second by 0·35 per 1,000. The numbers involved in both cases are small, so that concordance by the two methods does not necessarily follow. In fact, large populations are always necessary in such biological problems if anything approaching complete correlation is to be attained. However, if a large number of small districts are combined, closely corresponding results can be expected from the application of both methods.

TABLE IV. *Comparison of results of standardization by direct and indirect methods.*

	Crude death-rate per thousand population, 1911.	Standardizing factor.	Standardized Death-rates. By indirect method.	By direct method.
England and Wales .	14·595	0·9790	14·289	14·307
London . . .	15·152	1·0000	15·152	15·254
County Boroughs .	16·113	1·0263	16·537	16·606
Other Urban Districts .	14·035	0·9944	13·956	13·996
Rural Districts . .	13·083	0·8882	11·620	11·390

IV. LIFE TABLE DEATH-RATES.

The life table death-rate is the third measure in use. For reasons which follow from the assumptions on which life tables are constructed this measure must be taken as the most adequate at our disposal. It is assumed that an equal number of persons are born in each year and that the subsequent history of these persons is recorded year by year till all have died, uniform conditions as regards environment being postulated. As every one ultimately dies, the number of deaths in any one year is equal to the number of births, or in a very important extension of this statement, the number of persons dying above any individual age, in each year, is equal to the number attaining that age during the same period.

This ideal in practice is only approximately attained. If a population could be observed in which the same diseases were present in the same amount year by year, and if the births were regularly equal to the deaths and if there was no migration it might be possible, possessing statistics of such a community for a series of years, to deduce direct conclusions. But the conditions under which statistics can be collected never have presented such favourable features. Thus environment varies from time to time according to the zeal of the administrator, and during the present generation there has been on the whole an immense improvement in hygiene. Persons born in one environment have lived their lives in constantly changing circumstances and consequently the data collected do not necessarily describe the effect of the conditions present at the epoch of collection, but the sum of the effects of a changing complex. In practice, however, such data alone are at our disposal.

The term life table death-rate, as used in the succeeding pages, must be strictly defined. It is taken to signify the ratio of the number of deaths of persons above any defined age to the number living above that age in a stationary population. If the whole population be considered it refers to all persons from birth and upwards. It is easy to see that the healthier the district, corre-

spondingly fewer deaths occur at each of the earlier ages of life, and consequently a small death-rate implies a relatively larger population at high ages. The converse of this is that in an unhealthy district the number of persons reaching high ages is small. It is immediately obvious that the number of the younger individuals in such a population bears a higher ratio to the number of the elderly than in the previous case. The difficulties introduced by standard populations where the proportion of the young on account of the high birth rates in last century in general exceeds the proper proportion of the old is thus avoided. Had the construction of a life table been easy no one would have used a standardized death-rate. The latter can at best be described as no more than a *pis aller*.

A life table death-rate has, however, other properties. It is obvious that the average number of years of life after birth or after any age, known technically as the expectation of life, will be the reciprocal of the life table death-rate. Death-rates, life table or other, are usually defined by a number per 1,000, hence the average life or the expectation of life above any age will be given by dividing the number 1,000 by the life table death-rate. The lower the life table death-rate therefore the greater the mean age at which the individuals die. To return to Sir B. W. Richardson : his death-rate of 8 per thousand means that those born reach an average age at death of one hundred and twenty-five years. That such a demand suggests the superman seems sufficiently evident.

The definition of a life table death-rate as given above requires some comment. The definition is true even if the actual distribution of deaths in age periods be assumed to vary according to the most fantastic rules. In a population distributed according to experience the average age at death in many cases is about fifty years. This average age, however, is equally easily attained if half the persons born die at birth and the other half live to the age of 100 years. No one, however, could take a life table death-rate as a criterion of comparison did such distributions of deaths as that just suggested occur. What is actually found is that certain limited variations about a norm are possible and that these variations obey very definite laws. The chief life tables used in the discussion are given in Table V.

This section cannot close without some comparison between standardized death-rates and life table death-rates to illustrate one specific disadvantage of using standardized death-rates. This is best seen by taking specific examples (Table V). The standardized death-rate of the males in the healthy district life table (H_3) is observed to be 13·49. The life table death-rate is 18·91. A death-rate of 13·49 gives, however, on a stationary population a mean life of $\frac{1,000}{13·49}$ or 74 years, a figure hardly conceivable if the observed properties of life represent anything which is fundamental. Manchester (M_1), on the other hand, has a corrected death-rate of 27·94 per 1,000. The expectation of life at birth is 34·71 years, giving a death-rate of 28·81 on a stationary population. In other words, the variation of the standardized death-rate is from 13·5 to 27·94, the extremes being in the ratio of nearly one to two. The corresponding range of

TABLE V. *Showing the districts and dates of the life tables used in the discussion with symbols of reference and with the standardized and life table death-rates in each district for comparison.*

No.	District		Authority	Dates	Symbol.	Standardized death-rates.		Life table death-rates.	
						Males.	Females.	Males.	Females.
B 1	England		Farr	1838–1851	E_2	22·37	21·14	25·06	23·90
B 2	,,	Healthy Districts	,,	1849–1851	H_1	16·03	15·95	20·59	20·22
B 3	England		Ogle	1871–1880	E_4	21·64	19·40	24·18	22·41
B 4	England		Tatham	1881–1890	E_5	19·79	17·74	22·90	21·19
B 5	,,	Healthy Districts	,,	,,	H_2	14·26	13·40	19·42	18·50
B 6	Brighton		Newsholme	,,	B_1	19·70	16·05	22·94	20·41
B 7	Manchester		Tatham	,,	M_1	27·94	24·46	28·81	26·02
8	,,	Township	,,	,,	M_2	35·90	30·36	34·75	30·61
9	,,	Outlying Districts	,,	,,	M_3	24·85	22·21	26·24	24·05
10	Oldham		Tattersall	,,	O	27·91	24·27	27·12	24·54
B*11	England		Tatham	1891–1900	E_6	19·32	17·14	22·66	20·93
B*12	,,	Healthy Districts	,,	,,	H_3	13·49	12·49	18·91	17·95
B*13	London		Murphy	,,	L_1	21·82	18·70	24·40	22·06
14	Brighton		Newsholme	,,	B_2	18·62	15·43	22·26	19·93
15	Salford		Tattersall	,,	S_1	27·42	24·63	30·03	27·17
*16	England		King	1901–1910	E_7	16·35	14·32	20·61	19·09
*17	London		Murphy	,,	L_2	17·42	14·70	21·39	19·45
18	Salford		Tattersall	,,	S_2	21·54	19·19	24·83	22·42
*19	England		King	1910–1912	E_8	14·55	12·70	19·42	18·07
*20	London		,,	1911–1912	L_3				
*21	County Boroughs		,,	,,	C	Information not given.			
*22	Urban Districts		,,	,,	U				
*23	Rural Districts		,,	,,	R				

Index for Easy Reference.

Symbol.	No.	Symbol.	No.	Symbol.	No.	Symbol.	No.
B_1	6	E_6	11	L_1	13	O	10
B_2	14	E_7	16	L_2	17	R	23
C	21	E_8	19	L_3	20	S_1	15
E_2	1	H_1	2	M_1	7	S_2	18
E_5	3	H_2	5	M_2	8	U	22
E_4	4	H_3	12	M_3	9		

NOTE.—The tables marked with an asterisk are those used by Mr. Finch and myself for the calculation of the expectation of life. Those marked B are tables used in my first investigation (see Sect. VII).

the life table death-rates is 18·9 to 28·8, a difference very much less. As will be seen later, there is good reason for considering the second measure as much the most useful. In both these cases the population has a higher birth-rate than death-rate. If the converse be the case, the life table death-rate is lower than the standardized death-rate. Thus in the Liverpool registration district 1891–1900 the life table death-rate is 35·3 as against a standardized death-rate of 37·9 per thousand. The standardized death-rate as an independent measure of health is thus open to some objection except in the hands of those who know its limitations.

V. Methods suggested by Farr and Pearson.

There is, however, another method of approaching the problem used so far back as 1875 by Dr. Farr and that is to calculate the actual number of deaths due to disease in stationary populations. This assumes that life as represented by a large corpus of individuals obeys laws which show their existence by calculable responses to different hygienic circumstances. In the supplement for the decade 1861–1870 Dr. Farr gives a series of tables showing how persons living in certain different environments would die. This information is given for the whole of England and Wales ; for the healthy districts of England and Wales, and also for the Liverpool district. A specimen of his work is given in the accompanying table (Table VI). This method presents great advantages. The difficulty of the application of the method, a difficulty already alluded to, is that the necessary tables required for the discrimination of the different types of response to disease at different ages and in different environments had not been constructed. Now, however, that many life tables have been calculated and the process of making rough life tables has been so much improved, it is quite certain that the use of this method will supply in many cases the only figures on which it is safe to found a theory of mortalities. For instance, it will be possible to eliminate to a great extent the difficulties which arise on account of the different rates at which individuals grow old in town and country, differences which determine great alterations in the age incidence of disease. It is little use to apply statistical tests to decide whether differences in the age incidence of a disease in different environments are real or not. What is important is to settle whether such differences in age incidence imply that a disease is present in a greater or lesser amount.

The same salient of attack nearly thirty years ago appealed to Professor Karl Pearson, though his method of considering the problem at that moment was very different. Professor Pearson analysed the distribution of the deaths on the theory that special groups of deaths properly belong to corresponding periods of life. Thus some diseases are specially characteristic of infancy, some of childhood, some of adolescence, some of middle life, and some of old age. These groups overlap. In this way he describes in close accord with the facts how every one is subject to a series of specific age group risks. Professor Pearson's method introduced a new conception, but it must be criticized in that the analysis used by him referred only

to the types of curves he thought fundamental. These curves can be shown to be insufficient to describe the known processes of life. Though the method fails in this regard, yet when the necessary clearing of the ground has been accomplished and the lines on which it may be developed become better defined, and in addition when some agreement has been established as to what constitute age group risks of life, the mechanism which underlies the changes in the number of deaths in different environments at each age period will come within the range of competent mathematical analysis.

Professor Pearson's diagram (Diagram I) is rather inaccessible. It is reproduced here on a somewhat different scale, which I think illustrates the theory more clearly than the original diagram.

There is, however, one other measure derivable directly from Farr's conception which requires to be considered. It might be proposed to estimate how many persons living at a definite age in a given environment may be expected to die of some specific disease during their future life. Thus we might compare different districts by stating the percentage of persons reaching the age of 15 years who afterwards die of any disease. An example of this method of estimating the amount of disease in relation to cancer will be given later, but as yet none of the necessary spade work has been done, and until the possibilities of this criterion have been explored its use will be quite unsafe.

VI. Comparison of Death-rates at Different Ages.

The comparison of death-rates at different ages was first introduced by Dr. Farr in his article on ' Vital Statistics ' in McCulloch's *Statistical Survey of the British Empire*, and much further developed in the Decennial Supplement relating to the years 1861–1870.

In this supplement Dr. Farr collected the registration districts into seven groups, starting with 53 healthy districts in which the crude death-rate ranged from 15 to 17 per 1,000 and ending up with the Liverpool district in which the crude death-rate was 39 per 1,000. For each of these groups of districts he gives full details of the populations and deaths. Choosing the group of 53 districts with the lowest mortalities as the standard, he assumed that at each age period the death-rates in the first group of districts should be represented by 100 and with such a basis he calculates the relative mortalities in each several district in relation to the mortalities in the healthy districts. It is now recognized that in a matter like this it is much better to keep the sexes separate. While, therefore, Dr. Farr's figures are reproduced, the figures for the two sexes calculated from the original data are shown separately (Table VII).

The criticism of the results divides itself into two parts. The first concerns the ages from birth to 15 years, the second from 15 years and upwards. The first division will be more fully considered later, but one point must be noted. Under 5 years of age females are more affected by unhealthy surroundings than males, though from 5 years and upwards the converse phenomenon is observed.

Starting at the age of 15 years, it is to be observed that among males the maximum effect produced by unhealthy conditions occurs between the ages of 45 and 55 years, the mortality increasing with
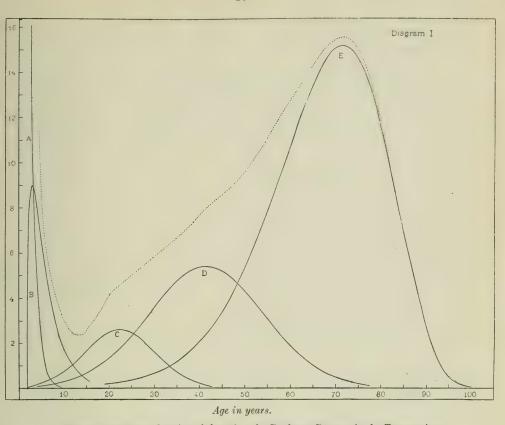
TABLE VI. *Table of mortality derived from the English life table, showing of what diseases and at what ages 1,000,000 liveborn children may be expected to die.*

The Table shows also, according to the English Life Table, the Annual Births being 1,000,000; the Annual Deaths 1,000,000; the Deaths at the respective Ages and of the respective Causes out of a Population of 40,858,184, enjoying a Mean Life-time of 40·858 years.

Ages	All Ages.	0–	5–	10–	15–	20–	25–	35–	45–	55–	65–	75–	85 and upwards.
DEATHS FROM ALL CAUSES	1,000,000	263,182	34,309	17,946	21,813	28,705	62,052	69,078	81,800	112,086	147,905	122,559	38,565
TOTAL ZYMOTIC DISEASES. Order 1	175,619	87,099	19,256	6,555	4,717	4,554	7,918	7,616	8,101	9,795	11,256	7,229	1,523
ZYMOTIC DISEASES. Order 1:													
1. Small-pox	6,521	3,331	833	244	291	456	624	347	210	113	53	16	3
2. Measles	12,865	11,507	1,080	127	39	29	41	23	11	5	2	1	—
3. Scarlatina	30,021	17,959	8,743	1,901	493	283	330	162	80	45	19	6	—
4. Diphtheria	4,945	2,425	1,364	464	165	100	125	91	74	68	47	19	3
5. Whooping-cough	15,161	14,424	682	35	6	2	4	2	2	2	2	—	—
6. Typhus	38,107	5,401	4,036	2,842	2,907	2,696	4,197	3,777	3,749	3,822	3,233	1,287	160
7. Diarrhoea and Dysentery	34,366	20,344	427	154	141	244	664	776	1,115	2,162	3,883	3,551	905
8. Cholera	6,155	1,129	382	173	134	215	640	781	829	865	688	281	38
9. Other Zymotic Diseases. Order 1	27,478	10,579	1,709	615	541	529	1,293	1,657	2,031	2,713	3,329	2,068	414
FIVE CONSTITUTIONAL DISEASES:													
10. Cancer	21,311	71	35	31	58	100	682	2,290	4,583	5,998	5,122	2,040	301
11. Scrofula and Tabes	14,106	8,115	1,100	811	633	541	815	576	542	511	361	93	8
12. Phthisis	114,417	4,469	2,139	3,526	9,074	13,785	27,134	22,404	16,468	10,445	4,294	627	52
13. Hydrocephalus	11,252	9,296	1,363	362	84	32	36	24	20	18	12	5	—

DESCRIPTION OF TABLE VI

This Table is a portion selected from a series of tables given by Dr. Farr in the Supplement of the Registrar-General for the decade 1861–1870, to illustrate his method of comparing different districts by following from birth to death a definite number of individuals and showing of what diseases they may be expected to die. A development of this method seems to be the only way to obtain accurate information with regard to the amount of some diseases.

Age in years.

This diagram is a re-drawing of that given by Professor Pearson in the *Transactions of the Royal Society* in 1894. The dotted curve shows the number of deaths at each age as given by the life table for England and Wales for the decade 1881–1890. The curves in continuous line represent the distribution of the deaths as suggested by Professor Pearson. The first curve (A) describes the mortality due to infantile diseases. The commencement is not shown, on account of the scale of the diagram. The great bulk of deaths in this group occur before the age of two years, and it ceases to be a factor of any importance by the age of nine years. The second curve (B) shows the mortality due to diseases of childhood; the maximum mortality in this group is at the age of three years : the diseases comprehended in this group cease to be of any importance by the age of fifteen years. The third curve (C) shows the mortality due to diseases of youth : the maximum number of deaths occur here at the age of twenty-two and a half years. The mortality due to diseases of middle life (D) has its maximum at forty-one and a half years, and the mortality due to diseases of old age (E) at sixty-seven years. When deaths in these different groups are added together the sums approach with extreme closeness the observations.

The equations of the curves are as follows :

A.	Infantile Mortality.	$y = 236(x + \cdot 75)e^{-\cdot 75x}$	origin at birth.
B.	Mortality of Childhood.	$y = 9(1 + x)^{\cdot 3271}e^{-\cdot 3271x}$	origin at 3 years.
C.	Mortality of Youth.	$y = 2\cdot 6e^{\frac{-x^2}{121\cdot 68}}$	origin 22·5 years
D.	Mortality of Middle Age.	$y = 5\cdot 4e^{\frac{-x^2}{327\cdot 68}}$	origin 41·5 years.
E.	Mortality of Old Age.	$y = 15\cdot 2(1 - \dfrac{x}{35})^{7\cdot 7525}e^{\cdot 2215x}$	origin 71·5 years.

where y is the number of deaths and x the distance from the origin measured in years.

TABLE VII. *Showing the relative mortality, 1861–1870, at twelve age periods in eight groups of districts of England and Wales, the deaths at each age in 53 healthy districts being represented by 100.*

Mortality range :

Age period.	15–17. In 53 healthy districts.			18–20. In 345 districts.			21–23. In 137 districts.			24. In London.		
	Persons.	Males.	Females.	Persons.	Males.	Females.	Persons.	Males.	Females.	Persons.	Males.	Females.
0–5	100	100	100	126	124	128	167	164	170	216	210	224
5–10	100	100	100	110	109	111	140	141	139	165	167	163
10–15	100	100	100	111	109	112	131	138	124	115	124	107
15–20	100	100	100	108	110	108	123	137	113	97	121	80
20–25	100	100	100	109	108	111	118	121	116	95	110	82
25–35	100	100	100	109	106	111	120	118	123	118	131	105
35–45	100	100	100	104	103	105	121	123	119	151	172	129
45–55	100	100	100	104	104	104	123	127	119	174	190	156
55–65	100	100	100	105	106	103	125	130	120	171	185	156
65–75	100	100	100	102	103	101	118	122	114	143	152	133
75–85	100	100	100	102	103	100	110	111	108	122	128	116
85 +	100	100	100	110	111	109	112	113	110	111	112	109
All ages	100	100	100	113	112	114	129	130	128	144	151	137

Mortality range :

Age period.	24–26. In 47 districts.			27–30. In 9 districts.			32. In Manchester district.			39. In Liverpool district.		
	Persons.	Males.	Females.	Persons.	Males.	Females.	Persons.	Males.	Females.	Persons.	Males.	Females.
0–5	217	212	223	251	244	260	296	284	310	369	349	394
5–10	166	168	164	189	196	183	231	250	212	286	294	279
10–15	141	158	125	140	157	125	170	190	152	177	195	161
15–20	127	150	111	142	187	108	150	196	115	152	197	118
20–25	116	117	115	124	139	109	140	156	125	167	190	144
25–35	120	117	123	141	159	123	166	177	156	225	241	208
35–45	132	137	127	162	181	142	214	233	194	272	302	243
45–55	146	152	139	184	199	167	249	255	242	318	323	312
55–65	154	161	146	177	186	167	244	253	235	284	299	269
65–75	138	144	132	155	163	146	193	199	186	204	219	189
75–85	124	129	119	132	138	126	148	159	137	139	147	129
85 +	116	120	112	116	119	112	123	142	102	99	103	95
All ages	146	149	144	165	172	158	194	201	187	228	233	223

each increase of the crude death-rate until in the Liverpool district the death-rate at these ages is three times that found when the healthy districts are taken as a standard. From this age period the ratio gradually decreases until at the ages of 85 and upwards the mortality is essentially the same no matter whether town or country be examined. Further, the ratio of the mortalities between 15 and 20 years of age is considerably less relatively than that between the ages of 45 and 55 years, yet in the unhealthy districts it rises to nearly twice that

Age in years.

In this diagram the mortalities of the rural, urban, and county death-rates at ages 15 and upwards are compared for the years 1911-1912. The death-rate at each age period in the rural districts has been taken as the standard and is denoted by the line marked unity. The curve (B) represents the ratio of the death-rates in the urban districts to that of the rural districts. Thus at the age period 50-55 years the reading 1·34 from the scale indicates that the death-rate at these ages in the urban districts is 1·34 times that in the rural. The curve (A) represents the same phenomena for the county boroughs. The death-rate at the same age period is found to be 1·74 times or nearly twice what it is in the rural districts.

in the healthy. Females considered separately show some differences : unlike males it is found that at the age of 15-20 years there is little difference between town and country. The relative mortality progressively increases until between 45 and 55 years the difference between the healthy and the unhealthy districts is as one to three. From this age-period the ratio regularly declines till it becomes, within the limits of random error, unity at the ages of 85 years and upwards.
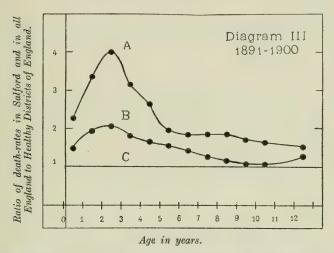
These figures refer to data collected more than fifty years ago. A corresponding series of ratios, however, calculated from the figures given in the supplement of life tables constructed by Mr. King and issued by the Registrar-General, demonstrate that the same conditions still hold. In this case the life table death-rates for the rural districts selected by Mr. King have been taken as the norm of life in healthy conditions. The age periods illustrated range from 15 to 95 years. The results are given in the accompanying table (Table VIII) and in part illustrated in the diagram (Diagram II). Other comparisons are given in Table IX.

TABLE VIII. *Showing the relative mortality among males and females at different ages in various life tables, the deaths at each age in the rural districts being represented by 100.*

MALES.

Age.	Aggregate of rural districts, 1911–1912.	Aggregate of urban districts, 1911–1912.	Aggregate of county boroughs, 1911–1912.	County of London, 1911–1912.	English Life table No. 8, 1910–1912.	English Life table No. 7, 1901–1910.
15	100	120	130	113	109	121
20	100	109	121	103	112	122
25	100	103	120	107	108	122
30	100	103	122	124	112	132
35	100	113	149	150	126	147
40	100	117	158	167	131	151
45	100	124	169	177	138	155
50	100	134	174	178	141	158
55	100	134	170	170	141	154
60	100	133	163	157	135	144
65	100	129	151	143	129	135
70	100	125	144	130	119	123
75	100	117	131	120	112	116
80	100	106	117	113	108	107
85	100	102	102	102	102	102
90	100	95	99	97	97	104
95	100	84	100	96	88	103

FEMALES.

Age.	Aggregate of rural districts, 1911–1912.	Aggregate of urban districts, 1911–1912.	Aggregate of county boroughs, 1911–1912.	County of London, 1911–1912.	English Life table No. 8, 1910–1912.	English Life table No. 7, 1901–1910.
15	100	103	115	95	103	111
20	100	93	106	80	96	106
25	100	92	103	83	96	109
30	100	93	104	90	99	116
35	100	101	123	109	108	128
40	100	110	139	132	120	139
45	100	123	152	151	130	147
50	100	122	150	145	128	142
55	100	117	144	135	123	137
60	100	123	143	129	122	134
65	100	116	138	122	120	127
70	100	117	133	115	114	123
75	100	113	125	107	108	115
80	100	108	118	107	108	108
85	100	104	110	107	102	107
90	100	94	101	98	96	104
95	100	102	98	104	99	105

It will be noticed that the maximum ratios between the death-rates occur about 45 to 50 years of age, and that though in different

districts there are slight differences in the curve, essentially the same phenomena are found throughout. It is on individuals at middle age that environment tells most severely. The reactions to the surroundings at different ages are, however, very closely correlated, as will be shown in Section X.

The behaviour of life in different environments under 15 years of age also obeys laws of its own. Here quinquennial groups are no longer sufficient. The data must be examined from year to year ; while in the earliest period of life, differentiation from month to month is required. Dealing first with the larger aspect of the matter, the accompanying diagram is given to illustrate how environment affects life at these ages (Table IX and Diagram III). The healthy district life table for the decade 1891–1900 has been taken as the

Age in years.
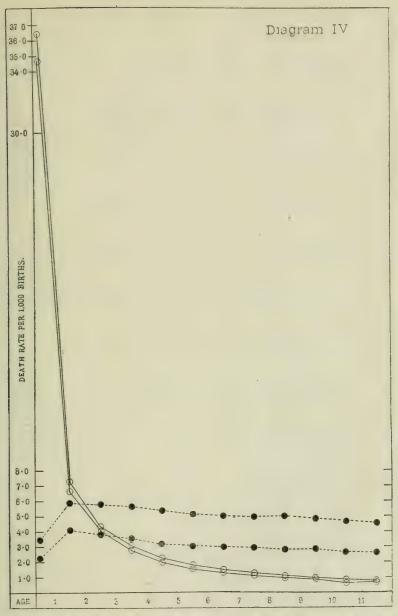
In this diagram the same phenomenon is shown for the ages under 15 years of age. The base line in this case illustrates the death-rates in the healthy districts of England for the decade 1891–1900. The curve marked (B) is the comparison of England as a whole with the healthy districts, and the curve (A) the same comparison for Salford. It will be noticed that it is between the ages of 2 and 3 years that the greatest amount of relative injury is done.

standard since Mr. King does not give any information in his rural district life table for the years 1910–1912 for ages below that of 12 years ; the first death-rate has been taken as 100 as in the case of adult life. From the comparison it appears that child life is unequally affected by the environment. Though the large infantile mortality in cities impresses on account of its size it is not at this age that the chief relative damage is to be seen. Environment acts progressively more and more unfavourably until the age of 2 years is reached, as may be medically verified by those who see large numbers of young children drawn from slum life. In all the curves of comparison, both those shown in the diagram and those not shown, the same phenomenon is observable. The ratio rises from birth to 2 years of age and then falls until in the neighbourhood of the age of 5 years a ratio is reached approximately equivalent to that experienced

TABLE IX. *Showing the relations of death-rates at different ages in different districts to those in the healthy districts of England, 1891–1900.*

Death-rates at different ages.   *Ratio of death-rates in several life tables to those of H_3.*

Age.	H_3. 1891–1900.		E.6 1891–1900.		Scotland. 1891–1900.		Salford. 1891–1900.		Manchester. 1881–1890.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
0	132·074	101·327	1·46	1·52	1·21	1·26	2·29	2·42	1·66	1·73
1	28·500	26·421	1·92	1·92	1·91	1·95	3·39	3·59	3·26	3·11
2	10·100	10·355	2·08	1·96	2·22	2·14	4·00	3·67	3·72	3·50
3	7·386	7·093	1·80	1·89	1·81	1·91	3·11	3·14	3·31	3·28
4	5·787	5·657	1·68	1·70	1·62	1·72	2·63	3·21	2·95	3·08
5	4·551	4·489	1·57	1·58	1·45	1·51	1·94	1·76	2·86	3·06
6	3·680	3·662	1·42	1·43	1·51	1·61	1·82	1·92	3·01	3·17
7	2·999	3·037	1·28	1·29	1·59	1·67	1·84	1·99	3·16	3·23
8	2·504	2·588	1·17	1·18	1·61	1·73	1·84	1·93	3·22	3·21
9	2·165	2·300	1·10	1·10	1·62	1·68	1·71	1·83	3·21	3·06
10	1·966	2·139	1·09	1·08	1·62	1·69	1·62	1·64	3·08	2·83
15	2·376	2·913	1·29	1·05	1·63	1·60	1·52	1·24	1·79	1·36
20	3·793	3·981	1·21	1·04	1·65	1·43	1·74	1·13	1·46	1·27
25	4·939	4·491	1·15	1·12	1·47	1·46	1·52	1·25	1·69	1·66
30	5·286	5·021	1·27	1·23	1·45	1·63	1·54	1·58	2·23	2·03
35	6·261	5·757	1·44	1·36	1·50	1·64	1·59	1·90	2·50	2·22
40	7·569	6·823	1·58	1·47	1·54	1·54	2·51	2·14	2·65	2·26
45	9·323	7·834	1·60	1·50	1·58	1·52	2·67	2·41	2·70	2·45
50	12·545	10·215	1·56	1·47	1·52	1·53	2·42	2·39	2·53	2·47
55	16·551	14·108	1·57	1·45	1·71	1·50	2·42	2·41	2·53	2·42
60	24·946	21·894	1·47	1·36	1·48	1·35	2·49	2·27	2·30	2·16
65	36·387	32·355	1·40	1·32	1·38	1·37	2·17	2·04	2·20	2·12
70	58·545	52·270	1·28	1·23	1·23	1·17	1·72	1·80	1·90	1·82
75	95·095	85·099	1·17	1·15	1·17	1·05	1·99	1·98	1·60	1·56
80	151·442	134·717	1·09	1·09	0·96	0·99	1·07	0·96	1·36	1·32
85	234·018	206·615	1·02	1·04	0·95	0·99	0·98	1·52	1·18	1·13
90	349·364	306·353	0·98	0·99	1·08	1·06	1·06	0·78	1·06	0·96
95	503·268	439·205	—	—	—	—	—	—	—	—
100	694·444	608·696	—	—	—	—	—	—	—	—

The death-rates in the first column are obtained by dividing the number of deaths occurring at each year of age by the mean population living in that year.

Diagram IV

DEATH RATE PER 1,000 BIRTHS.

In this diagram two sets of curves are given. The first in continuous line shows the curve of the death-rate from those diseases which are specially due to instability— premature birth, convulsions, &c., and the second in dotted line to the diseases which are due to infection. It will be observed that in the first class the phenomenon observed in the town and in the country differ very slightly. The relation of the deaths from infectious diseases in the two classes of districts are, however, very different, the figures for the town being 60 per cent. on the whole more than those of the country.

TABLE X. *Showing the mortality per thousand living births of children during the first twelve months of life in the urban and rural registration counties from the diseases which chiefly affect the first few months of life, 1906–1910.*

URBAN REGISTRATION COUNTIES.

	Under one month.	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–
Premature Birth	17·80	1·29	0·36	0·10	0·05	0·03	0·01	0·01	0·01	0·00	0·00	0·00
Congenital Defects	4·98	0·68	0·36	0·19	0·15	0·10	0·08	0·07	0·05	0·04	0·04	0·04
Starvation	0·15	0·17	0·13	0·10	0·07	0·04	0·03	0·02	0·02	0·01	0·01	—
Atrophy, Debility, Marasmus	6·38	2·26	1·57	1·16	0·76	0·54	0·42	0·31	0·27	0·22	0·16	0·16
Injury at Birth	0·89	0·01	0·00	0·00	—	—	—	—	—	0·00	0·00	—
Convulsions	4·25	1·73	1·18	0·90	0·68	0·51	0·40	0·35	0·25	0·21	0·19	0·17
Suffocation	0·58	0·47	0·35	0·22	0·15	0·08	0·05	0·03	0·02	0·02	0·01	0·01
Other Causes	1·40	0·68	0·42	0·42	0·43	0·53	0·52	0·49	0·48	0·48	0·40	0·39
Total	36·43	7·29	4·37	3·09	2·29	1·83	1·51	1·28	1·10	0·98	0·81	0·77

RURAL REGISTRATION COUNTIES.

	Under one month.	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–
Premature Birth	16·53	1·07	0·29	0·11	0·06	0·01	0·01	0·01	0·01	0·00	0·00	0·00
Congenital Defects	4·19	0·63	0·29	0·18	0·12	0·10	0·09	0·08	0·05	0·05	0·03	0·05
Starvation	0·10	0·13	0·11	0·04	0·03	0·03	0·02	0·01	0·01	0·01	0·01	0·01
Atrophy, Debility, Marasmus	7·31	2·25	1·42	0·99	0·55	0·37	0·32	0·22	0·17	0·16	0·11	0·09
Injury at Birth	0·78	0·01	0·00	—	0·00	0·00	—	—	—	—	—	—
Convulsions	4·04	1·59	1·28	0·91	0·70	0·48	0·39	0·32	0·25	0·22	0·20	0·16
Suffocation	0·24	0·14	0·14	0·10	0·07	0·03	0·02	0·02	0·01	0·01	0·01	0·01
Other Causes	1·43	0·80	0·53	0·47	0·49	0·54	0·51	0·53	0·45	0·43	0·29	0·34
Total	34·62	6·62	4·06	2·80	2·02	1·56	1·36	1·19	0·95	0·88	0·65	0·66

The Urban Registration Counties are :

Glamorganshire
Lancashire
London
Middlesex
Monmouthshire
Northumberland
Nottinghamshire
Staffordshire
Warwickshire
East Riding with York
West Riding.

The Rural Registration Counties are :

Anglesey
Brecknockshire
Buckinghamshire
Cambridgeshire
Cardiganshire
Carmarthenshire
Cornwall
Carnarvonshire
Denbighshire
Flintshire
Herefordshire
Huntingdonshire
Lincolnshire
Merionethshire
Montgomeryshire
Norfolk
Oxfordshire
Pembrokeshire
Radnorshire
Rutlandshire
Shropshire
Somersetshire
Suffolk
Westmorland
Wiltshire.

under the age of one year. The actual minimum occurs in different places at different ages, a difference often depending on different epidemic conditions, but a second maximum at the age of 8 years found in Manchester in the decade 1881–1890, though possibly largely due to severe epidemics of scarlet fever, is yet probably due to defect in statistical method, while the high ratios found between the ages of 10 and 15 years in Scotland in comparison with those experienced in England are definitely due to an excess of phthisis of early adult life.

The problem of infancy, however, presents some other points demanding careful consideration (Table X and Diagram IV).

The relation of infantile mortality to environment has hardly yet received the attention it deserves. The death-rate is certainly dependent on three main factors : the first, the shock of birth ; the second, the instability of the nervous, digestive, and circulatory systems of the young child ; the third, the presence or absence of infection. The first and second of these two divisions are independent of environment to an extent which could hardly be expected. To illustrate this, two tables have been compiled from Dr. Stevenson's data contained in the last decennial supplement issued by the Registrar-General. The first of these tables refers to those groups of disease in which the mortality decreases from birth and upwards. The four most important of these causes of death are premature birth, atrophy, debility and marasmus, congenital malformations and convulsions. These causes account for the specially high mortality immediately after birth and for a considerable though decreasing mortality till the end of the first year. The death-rates are given per 1,000 for the urban counties and rural counties severally. It will be observed that from these causes of death the mortality in the first three months of life is in the urban counties only 6 per cent. greater than that in the rural counties, while in the last three months of the first year the mortality in the urban counties has only increased till the ratio between the mortality is 17 per cent. greater in the urban than that in the rural counties. This cannot be esteemed as anything but a very surprising result. It seems quite definite that there is a group of diseases which apparently kill quite independently of the environment either of the child or of the mother. In fact, in the rural counties the deaths from these conditions amount to very nearly half the total mortality. Considering these figures for the town and for the country it seems obvious that this group of deaths depends on influences which act accidentally. The child in the womb is a true parasite protected against the vicissitudes of the mother and more or less independent even of her starvation or dissipation. How to act on such obscure relationships is a problem of great intellectual attraction, but, though the study of these conditions must be pursued, it affords little prospect of immediate profit.

With regard to the third group of diseases there is, I think, a quite different outlook. Examining the table (Table XI) which describes the range of deaths due to infection proper a totally different series of relationships is seen. Here in the first three months of life the mortality in the urban counties is 48 per cent. greater than in the rural counties, while in the last three months of the first year

it is 75 per cent. greater. It is this group of diseases that sanitation should attack with immediate effect.

In comparing the death-rates at different ages, however, some care is necessary. As has been seen in the diagrams and tables in later life the maximum effect of unhygienic surroundings occurs about the age of 50 years. Taking the data of life tables where large populations are dealt with, it is found that there is an almost perfect correlation between the death-rate at ages 50 to 55 years and the life table death-rate for all ages above 35 years : in other words the death-rate in that quinquennium may be taken as representing accurately the whole effect of environment on health in middle and advanced ages. When smaller populations are used the correlations are still large. For instance, taking the data referring to the counties of England for the years 1891–1900 the correlation between the death-rates at the age periods 45–55 years and 55–65 years and the life table death-rates at the ages above 35 years are respectively 0·967 and 0·980. It is thus possible from the death-rates at either of these age periods to calculate the life table death-rates within a range of $\frac{1}{2}$ per cent. Though this is true with regard to the later ages of life the same cannot, however, be said of the earlier ages. As we have seen, the maximum effect of bad environment in depressing health is between the ages of 2 and 3 years. But the death-rate at this age is no longer linearly related in the same way to the life table death-rate. For instance, if the infantile mortality be taken as the standard of health in a district, the death-rate at 2 years of age while increasing with the infantile mortality does not rise in such a manner that the relationship can be expressed by a straight line. The increase is slow at first, then much more rapid. It is, therefore, not safe in investigating the statistics of children's diseases to use age mortality figures for rigid correlation without making an initial investigation.

It would not be fair to pass to the next part of the argument without making a short historical note. Dr. Farr's last great work was his supplement to the thirty-fifth Annual Report of the Registrar-General, which was published in 1875. In this supplement practically every method which has been found of importance in the use of health statistics since that date is contained. It might have been expected that having done so much he would have carried his investigations further, but before there was time for that further collection of data necessary for the development of his ideas, he was driven by ill health to retirement and thus robbed of the fruit of his vision.

VII. THE CONNEXION BETWEEN LIFE TABLE AND STANDARDIZED DEATH-RATES.

From what has been said it is to be inferred that a life table death-rate is the criterion of ultimate importance, and that for many purposes unless such a death-rate is obtainable it is impossible to draw valid conclusions.

To demand life table death-rates, however, if these could only be obtained by calculating the required life table would be futile, as

TABLE XI. *Showing the death-rates per thousand living births among infants during the first twelve months of life in the urban and rural registration counties from the diseases which are due to infection, 1906–1910.*

URBAN REGISTRATION COUNTIES.

	Under one month.	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–
Measles	0·02	0·04	0·02	0·02	0·05	0·11	0·19	0·32	0·44	0·52	0·60	0·66
Scarlet fever	0·00	0·00	0·00	0·00	0·01	0·01	0·01	0·02	0·02	0·02	0·03	0·03
Diphtheria	0·01	0·01	0·01	0·01	0·01	0·01	0·03	0·03	0·05	0·06	0·07	0·07
Whooping-cough	0·11	0·42	0·42	0·38	0·36	0·37	0·40	0·42	0·47	0·45	0·45	0·47
Enteritis	0·25	0·38	0·42	0·38	0·34	0·29	0·24	0·19	0·17	0·15	0·13	0·12
Gastro-enteritis	0·20	0·29	0·31	0·30	0·28	0·23	0·20	0·16	0·14	0·13	0·11	0·09
Gastro-intestinal catarrh	0·07	0·11	0·10	0·09	0·07	0·06	0·04	0·03	0·03	0·03	0·03	0·02
Diarrhoea	0·53	1·26	1·54	1·71	1·59	1·41	1·28	1·14	1·02	0·91	0·77	0·70
Tuberculous meningitis	0·02	0·03	0·07	0·10	0·12	0·16	0·18	0·18	0·20	0·17	0·16	0·16
Tuberculous peritonitis	0·04	0·12	0·19	0·22	0·22	0·20	0·16	0·14	0·15	0·14	0·12	0·12
Other tuberculous diseases	0·03	0·06	0·10	0·13	0·13	0·12	0·12	0·12	0·12	0·12	0·12	0·14
Syphilis	0·26	0·27	0·19	0·13	0·08	0·05	0·03	0·02	0·02	0·02	0·02	0·01
Erysipelas	0·06	0·06	0·03	0·02	0·02	0·01	0·01	0·01	0·01	0·01	0·01	0·00
Rickets	0·00	0·01	0·02	0·03	0·03	0·04	0·04	0·05	0·06	0·06	0·07	0·07
Meningitis	0·09	0·11	0·13	0·16	0·19	0·22	0·22	0·22	0·20	0·21	0·18	0·17
Laryngitis	0·01	0·01	0·01	0·01	0·01	0·01	0·01	0·02	0·01	0·03	0·02	0·02
Bronchitis	0·99	1·49	1·06	0·92	0·78	0·73	0·68	0·66	0·64	0·58	0·54	0·49
Pneumonia	0·53	0·94	0·94	0·90	0·91	1·00	1·09	1·16	1·20	1·19	1·17	1·17
Gastritis, Gastric catarrh	0·23	0·29	0·27	0·22	0·19	0·13	0·11	0·10	0·07	0·07	0·05	0·04
Total	3·45	5·90	5·83	5·73	5·39	5·16	5·04	4·99	5·02	4·87	4·65	4·55

TABLE XI—continued.

RURAL REGISTRATION COUNTIES.

	Under one month.	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–
Measles	0·01	0·02	0·02	0·03	0·03	0·06	0·10	0·11	0·17	0·20	0·23	0·24
Scarlet fever	0·00	0·01	0·00	0·00	0·01	0·00	0·01	0·01	0·01	0·01	0·00	0·01
Diphtheria	0·00	0·01	0·01	0·00	0·01	0·01	0·01	0·02	0·02	0·02	0·02	0·04
Whooping-cough	0·13	0·49	0·44	0·44	0·35	0·33	0·35	0·36	0·36	0·39	0·33	0·38
Enteritis	0·18	0·28	0·26	0·25	0·16	0·17	0·13	0·13	0·09	0·09	0·07	0·06
Gastro-enteritis	0·16	0·26	0·28	0·25	0·22	0·18	0·14	0·12	0·13	0·11	0·07	0·07
Gastro-intestinal catarrh	0·04	0·06	0·06	0·04	0·04	0·03	0·04	0·01	0·02	0·01	0·01	0·00
Diarrhœa	0·31	0·63	0·56	0·64	0·57	0·54	0·42	0·40	0·29	0·30	0·24	0·22
Tuberculous meningitis	0·01	0·02	0·03	0·07	0·06	0·10	0·10	0·11	0·12	0·13	0·14	0·07
Tuberculous peritonitis	0·03	0·10	0·15	0·14	0·13	0·12	0·10	0·09	0·08	0·06	0·04	0·05
Other tuberculous diseases	0·02	0·06	0·08	0·08	0·12	0·09	0·07	0·09	0·11	0·09	0·12	0·11
Syphilis	0·12	0·10	0·09	0·06	0·04	0·04	0·03	0·02	0·01	0·01	0·01	0·01
Erysipelas	0·04	0·06	0·03	0·01	0·02	0·01	0·00	0·01	0·00	0·00	0·00	0·00
Rickets	0·00	0·00	0·02	0·03	0·02	0·02	0·04	0·05	0·04	0·03	0·08	0·09
Meningitis	0·02	0·04	0·09	0·11	0·11	0·11	0·10	0·12	0·09	0·13	0·10	0·08
Laryngitis	0·02	0·01	0·01	0·01	0·01	0·01	0·01	0·02	0·03	0·02	0·02	0·01
Bronchitis	0·66	1·01	0·82	0·63	0·58	0·46	0·48	0·46	0·47	0·42	0·40	0·40
Pneumonia	0·36	0·68	0·69	0·59	0·62	0·64	0·79	0·74	0·72	0·78	0·71	0·66
Gastritis, Gastric catarrh	0·17	0·25	0·24	0·18	0·13	0·09	0·09	0·04	0·07	0·05	0·03	0·04
Total	2·28	4·09	3·88	3·56	3·18	3·01	3·01	2·91	2·83	2·85	2·62	2·54

NOTE.—See Table X for list of Urban and Rural Registration Counties.

TABLE XII. *Giving the values of the constants required for obtaining the life table death-rates or the expectations of life from the standardized death-rates at each age and upwards, the standardized death-rates being calculated from the population given in the table.*

Age period.	Males. m	c	Δ	Females. m	c	Δ
0	0·68168	9·60	0·14	0·67905	9·37	0·11
5	0·47450	12·46	0·10	0·48971	11·89	0·12
10	0·45126	13·58	0·09	0·45154	13·15	0·12
15	0·45352	14·58	·0·11	0·45469	14·09	0·12
20	0·47543	15·33	0·10	0·47696	14·81	0·12
25	0·49846	16·13	0·08	0·48785	15·76	0·10
35	0·55201	17·87	0·12	0·51554	17·89	0·15
45	0·59426	20·54	0·19	0·56960	20·16	0·33
55	0·67588	22·09	0·55	0·65433	21·81	0·64

Age period.	Numbers in standard population, 1891–1900. Males.	Females.
0–5	59,052	59,468
5–10	56,000	56,289
10–15	53,521	53,550
15–20	49,986	50,814
20–25	44,106	49,419
25–35	74,159	81,938
35–45	57,412	61,276
45–55	41,980	45,629
55–65	27,212	31,184
65–75	15,026	18,596
75 and upwards	5,603	7,780

Age.	Population at each age and upwards. Males.	Females.
0	484,057	515,943
5	425,005	456,475
10	369,005	400,186
15	315,484	346,636
20	265,498	295,822
25	221,392	246,403
35	147,233	164,465
45	89,821	103,189
55	47,841	57,560
65	20,629	26,376
75	5,603	7,780

Equation of relation $D_x = mD_1 + c$
where D_x is the life table death-rate, D_1 the standardized death-rate, and Δ the square root of the mean of the squares of the differences of the actual and theoretical values.

NOTE.—The method of using this table is fully described in Sect. XXII.
The values of the constants are not those already given in the original paper but have been specially recalculated as some errors in the death-rates on which the original calculations were based have been discovered. The fits of the formulae are considerably more accurate than those originally given.
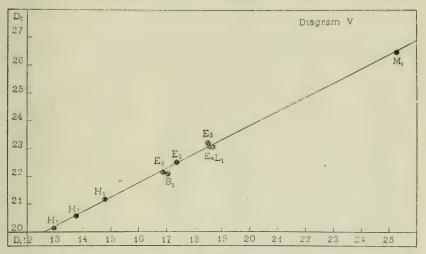
TABLE XIII. *Showing the comparison of the actual and theoretical life table death-rates obtained from the life tables and from the short method described in the text.*

	Age 0-				Age 15-				Age 35-				Age 55-			
	Males.		Females.		Males.		Females.		Males.		Females.		Males.		Females.	
	Act.	Theo.	Act.	Theo.	Act.	Theo.	Act.	Theo.	Act.	Theo.	Act.	Theo.	Act.	Theo.	Act.	Theo.
H_3	18·91	18·75	17·95	17·86	20·13	20·28	19·58	19·74	30·01	30·01	28·74	28·92	55·19	54·59	52·30	52·00
H_2	19·43	19·32	18·50	18·47	20·57	20·65	20·13	20·15	30·58	30·51	29·27	29·29	55·56	55·19	52·47	52·08
H_1	20·59	20·52	20·22	20·20	21·19	21·20	21·26	21·12	30·40	30·44	29·89	30·00	54·08	54·34	51·98	52·60
E_6	22·66	22·77	20·93	21·01	22·12	22·16	21·00	21·07	34·20	34·22	31·73	31·73	63·33	63·13	58·00	57·68
E_5	22·90	23·09	21·20	21·42	22·49	22·46	21·48	21·44	34·59	34·52	32·09	32·00	63·53	63·25	58·04	57·77
E_4	24·18	24·35	22·41	22·55	23·04	23·00	21·92	21·94	34·92	35·05	32·36	32·53	62·70	63·68	57·70	58·68
E_3	25·06	24·85	23·89	23·73	23·16	22·97	22·78	22·60	34·01	34·10	32·69	32·85	60·79	61·98	57·37	58·74
B	22·94	23·03	20·41	20·27	22·39	22·28	20·38	20·34	34·46	34·22	30·79	30·44	60·68	60·63	54·11	53·57
L	24·40	24·49	22·06	22·07	23·04	23·08	21·23	21·35	36·70	36·61	32·87	32·79	67·75	67·40	59·81	59·55
M	28·81	28·61	26·01	25·94	25·79	25·95	24·10	24·26	42·09	42·32	38·02	38·04	80·06	79·84	71·89	71·51

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the construction of a life table requires both skill and time. Two
questions therefore arise : first, is there any relation between
standardized death-rates and life table death-rates ; second, can life
tables sufficient for the necessary practical purposes be easily con-
structed ? In this section the first will be considered. The second
is discussed later.

This subject I entered upon for the first time in 1913, when I dis-
covered that standardized death-rates and life table death-rates
were directly related. In fact, life table death-rates can be at once
calculated within a very small range of error if the standardized
death-rates are known.

In this diagram the relationship of the life table death-rate to the standardized
death-rate is shown for the ages of 15 years and upwards with regard to ten life
tables. The very close agreement of the formula to the fact is to be noted.

It may be useful to recapitulate this work briefly. Certain life
tables (Table V, marked with the letter B) were chosen referring to
districts with a large range of mortality. The standard population
chosen was the mean population of England between 1891 and 1900.
Standardized death-rates were calculated for a series of ages from
birth and upwards : at birth, at five years, at ten years, &c., and
compared with the life table death-rates. It was found that at each
age linear relationships correct within a very small margin of error
held between the two series of death-rates. It is not necessary to
reproduce all the figures originally given, but the equations of relation
are reproduced (Table XII), and the close correspondence between
the standardized and the life table death-rates (Table XIII) is
shown at birth and at the ages of 15, 35, and 55 years for both males
and females. A diagram of the data (Diagram V) is also given for
the age of 15 years in males, one of the closest correspondence, though
in the majority of cases the error is very little greater.

Mr. Finch of Somerset House, repeating this work and using the
more recent life tables. deduces a new series of equations (Table XIV).

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TABLE XIV a. *Equations between the life table death-rates* (D_2) *and the standardized death-rates* (D_1).

Age.				In unit population $D_2 =$	In years.	% of mean value of true $\overset{o}{e}_x$
0	.	.	.	$0{\cdot}66986D_1 + 0{\cdot}00982$	0·17	0·36
5	.	.	.	$0{\cdot}46088D_1 + 0{\cdot}01249$	0·05	0·09
10	.	.	.	$0{\cdot}46547D_1 + 0{\cdot}01329$	0·05	0·11
15	.	.	.	$0{\cdot}48464D_1 + 0{\cdot}01402$	0·09	0·19
20	.	.	.	$0{\cdot}50105D_1 + 0{\cdot}01484$	0·09	0·20
25	.	.	.	$0{\cdot}52042D_1 + 0{\cdot}01569$	0·09	0·23
35	.	.	.	$0{\cdot}56361D_1 + 0{\cdot}01772$	0·08	0·27
45	.	.	.	$0{\cdot}60613D_1 + 0{\cdot}02039$	0·07	0·30
55	.	.	.	$0{\cdot}66883D_1 + 0{\cdot}02319$	0·06	0·35
65	.	.	.	$0{\cdot}77593D_1 + 0{\cdot}02336$	0·05	0·49
75	.	.	.	$0{\cdot}99695D_1 + 0{\cdot}00390$	0·04	0·65

TABLE XIV b. *Females. Equations between the life table death-rates* (D_2) *and the standardized death-rates* (D_1).

Age.				In unit population $D_2 =$	In years.	% of mean value of true $\overset{o}{e}_x$
0	.	.	.	$0{\cdot}66556D_1 + 0{\cdot}00967$	0·11	0·21
5	.	.	.	$0{\cdot}45584D_1 + 0{\cdot}01217$	0·01	0·02
10	.	.	.	$0{\cdot}45553D_1 + 0{\cdot}01299$	0·05	0·09
15	.	.	.	$0{\cdot}47319D_1 + 0{\cdot}01372$	0·10	0·21
20	.	. .	.	$0{\cdot}48993D_1 + 0{\cdot}01454$	0·10	0·22
25	.	.	.	$0{\cdot}50238D_1 + 0{\cdot}01545$	0·10	0·24
35	.	.	.	$0{\cdot}52935D_1 + 0{\cdot}01761$	0·11	0·33
45	.	.	.	$0{\cdot}55907D_1 + 0{\cdot}02068$	0·10	0·40
55	.	.	.	$0{\cdot}60759D_1 + 0{\cdot}02469$	0·07	0·40
65	.	.	.	$0{\cdot}68104D_1 + 0{\cdot}02950$	0·06	0·49
75	.	.	.	$0{\cdot}78216D_1 + 0{\cdot}03337$	0·06	0·81

NOTE.—This table has been calculated by Mr. Finch.

DESCRIPTION OF TABLE XIV

This table gives the values of the constants when the Census population for 1901 for England and Wales is used as a standard population. The figures have been calculated with the help of the data obtained from the life tables marked with an asterisk in Table V. The errors are given in years of life in the expectations.

The standard population is in this case taken as that given by the census of 1901 for England and Wales. The life tables used by Mr. Finch are of a higher order of accuracy, and are those marked with an asterisk in Table V. The errors existing in this case between fact and theory are very much smaller than those found in the original investigation.

VIII. THE CHOICE OF A STANDARD POPULATION.

As it has been found, first by myself and later by Mr. Finch, that the population of England and Wales at any date between 1890 and 1901 might be taken as a standard population to determine the true or life table death-rate, a discussion of the nature of the requirements of a standard population is obviously demanded.

It might be thought in the first instance that it would be possible. taking a selection of the most accurately constructed life tables as

the criterion of the facts, to assume that a series of standard popu-
lations at each age, taken at first as unknown, might be evaluated
by the process of least squares in comparison with the criterion
selected. This would necessarily be laborious, but that would not
be an objection as it could be done once for all. It is found, however,
on trial that this method gives rise to negative populations at certain
ages, a finding previously recognized by Professor Pearson and
Dr. Tocher in their work on cancer death-rates. Now it is not
I think advisable to work with negative populations. The assumption
is too artificial. Further, in calculating life table death-rates for
each different age from birth and upwards, a different set of age
period groups in the standard population is found necessary. A life
table death-rate at birth thus requires a different standard population
than that at fifteen years. The method, therefore, even if accurate
would be very laborious, and as absolute accuracy at all age periods
is impossible, a laborious method does not seem to offer any special
advantage.

The standard population used by myself has hitherto been that of
England and Wales for the decade 1891–1900. It was the standard
when I first became interested in these matters, and for comparative
purposes in my own work I did not wish to change. This is, however,
not a homogeneous standard. For the first twenty years of life the
numbers living are the survivors of a nearly constant number of
births. Above the age of twenty years those living in each succeeding
age period are the survivors from a number of births which decreases
approximately in a geometrical progression, the actual number of
births having roughly increased in a geometrical progression from
the beginning of the nineteenth century to the year 1875. The
question thus arises, what would happen if the standard population
were really a life table population derived from a number of births
increasing uniformly in a geometrical progression? Such a standard
population was accordingly calculated by multiplying each age group
in the life table population for the decade 1891–1900 by a factor
representing the numbers of births at each age period. It was found
using this standard that some improvement in the prediction of the
life table death-rates was obtained. The further question then
seemed to arise, did the method of King and Newsholme, in which
a specific life table population was chosen as a standard population,
offer a better approximation? To answer this a trial was made using
the life table population of England and Wales for the decade
1891–1900 as a standard population. Results, however, of inferior
accuracy were obtained. It was then suggested that as part of the
mechanism of the standard population which had given the best
results consisted of the geometric ratio into which a life table popu-
lation had been multiplied at each respective age group, perhaps
a standard population in which the numbers at each age period bore
a constant geometric ratio to those of each preceding age period
might be used advantageously. Such a population has a constant
death-rate, a fact which might have some bearing on the relationships
found. A standard population was therefore calculated so that the
number of survivors at 60 years of age was equal to one-tenth of the
persons born. It was found using this population that the results

were much less accurate than those based on the life table population. What was remarkable, however, in all these trials was the small difference made by these several changes.

Here the matter might well have rested had not the spirit of unrest demanded further inquiry. An arithmetical progression was therefore assumed as the law of decrease of population. With an arithmetical progression the slope of the progression does not matter ; if death-rates are applied to ordinates in the same position relatively to the time abscissae the magnification of populations and deaths is in an equal ratio. The standardized death-rates are thus not affected. The datum of importance is the age of the ultimate limit of life. Three limits of life were chosen—$77\frac{1}{2}$, $82\frac{1}{2}$, and $87\frac{1}{2}$ years respectively : for the first of these the populations at each age group of five years are in the ratio—15, 14, 13, &c., for the second 16, 15, 14, &c., leaving one survivor after the age of 75 years ; for the third 17, 16, 15, &c. Using these populations as standard populations, it is found that the most accurate results are obtained when the upper limit of life is taken as 82·5 years. The mean errors found in each case when life table death-rates with regard to the ten life tables given in Table V (marked B) are compared with the death-rates standardized in all the ways above described, are shown in the accompanying table (Table XV). It is curious to observe that De

TABLE XV. *Giving the standard error of the life table death-rates calculated upon different populations as described in the text.*

Standard populations.	Age.			
	0–	15–	35–	55
Population of England, 1891–1900 .	0·14	0·11	0·12	0·55
Life table population of England, 1891–1900	0·29	0·19	0·16	0·59
Life table population multiplied by the appropriate term of a geometrical progression . . .	0·17	0·12	0·11	0·54
Population in arithmetical progression	0·17	0·13	0·08	0·43
Population in geometrical progression	0·48	0·43	0·20	0·83

Moivre's arbitrary population designed in 1725 for insurance purposes, namely, that one person died in each year of life up to the limit of the age of 86 years, so closely corresponds to the type of standard population required to equate the standard death-rate and the life table death-rate. For the purposes for which the method was devised it proved a poor guide, but his intuition has not been in vain. His hypothesis comes back surrounded with a nimbus of convenience, and is thus a fine example of a solar myth.

The life tables, however, on which this investigation was first based are not wholly satisfactory, as they are not strictly comparable in method of construction. For inquiries into the length of the expectation of life based on data prior to 1890, however, the first found equations (Table XII) had best be used. Health conditions have, however, changed since last century in a manner which cannot be directly calculated. In the early days among other things there were large epidemics of cholera and typhus. Further bad water-

supplies, over-crowding, and dissipation were much more common during most of last century. In framing then a new set of equations to obtain the life table death-rates, it has been thought better to limit the calculations to the more recent life tables which Mr. Finch selected as the basis of his work (Table XVI). The standard errors

TABLE XVI. *Giving the constants required to calculate the life table death-rates from* the number of deaths *obtained by applying the death-rates at each age period to a standard population adjusted so as to be in arithmetical progression.*

| | MALES. | | | FEMALES. | | | | POPULATION ON ARITHMETICAL BASIS. | |
| | | | | | | | | Population at each age. | Population at each age and upwards. |
Age.	m	c	Δ	m	c	Δ	Age.		
0–	0·0047986	10·052	0·09	0·0046168	10·604	0·05	0–	16	136
5–	0·0036317	12·756	0·03	0·0039159	12·460	0·02	5–	15	120
10–	0·0044503	13·210	0·06	0·0043761	13·395	0·03	10–	14	105
15–	0·0050789	14·303	0·07	0·0052281	14·202	0·03	15–	13	91
20–	0·0061455	15·254	0·06	0·0063082	15·132	0·03	20–	12	78
25–	0·0076268	16·204	0·07	0·0077535	16·154	0·03	25–	21	66
35–	0·012322	18·546	0·09	0·012239	18·759	0·03	35–	17	45
45–	0·021530	22·017	0·12	0·020931	22·606	0·05	45–	13	28
55–	0·044486	26·720	0·13	0·043032	27·667	0 05	55–	9	15
65–	0·127236	31·954	0·25	0·121408	34·123	0·13	65–	5	6
75+	1·003635	2·823	0·99	0·876036	20·901	1·03	75–	1	1

NOTE.—It is to be noted that in this table the constants have been adjusted to obtain a life table death-rate directly from the number of deaths, thus saving the labour of calculating a standard death-rate for each age (Sect. XXII).

are added for comparison. It will be observed how small these become when the standard population formed in an arithmetical progression is used in combination with the most accurate life tables. This must be held to be a somewhat astonishing result. A population decreasing in a uniform manner has a law of increase of death-rate which has no analogy in life, yet it is found possible to obtain from this population, by a series of simple equations, the same results as by the more elaborate method of calculating a life table. The success of the method is, however, in keeping with the discovery that a life table death-rate could be calculated from a specific standard population. This standard, the mean population of England and Wales for the decade 1891–1900, is very nearly in an arithmetical progression, and that calculated from the life table population of the same epoch multiplied into a suitable geometrical progression still more so. It would seem, therefore, that Providence had a hand in furnishing at the proper time the data in the form most suitable to this work.

There is, however, one further point of interest in the matter. Examining the constants of the equations connecting the two death-rates, it is obvious that they do not progress from quinquennium to quinquennium in a uniform manner. There is between one five years and another a more rapid increase than between the succeeding similar periods. The differences fall to rise again. This is analogous to what is found in the life tables themselves as constructed. In these the third and fourth differences between the numbers surviving at successive ages oscillate slowly between positive and negative values.

It may be asked why, when such great accuracy can be obtained, a still greater accuracy is not possible ? The reasons for this I think have already been explained in the introduction, but there is one special reason which vitiates all the statistics, even those for the whole country. Between the ages of 15–30 years there is a great influx of young persons into the towns, from a healthy to unhealthy environ-ment. When town or country districts are considered separately this migration tends to raise the country death-rates at these ages. To take a special example, referring to the decade 1861–70, the death-rates at the ages from 10–25 years in London are lower than that of all England and Wales as a whole. It is not possible at present to make any attempt to evaluate the effect of this numerically, but the formulae as given do not in any case make a very great error in the expectation.

IX. FARR's LAW. THE RELATION OF DENSITY TO DEATH-RATE.

In Section IV the life table death-rate was selected as the best measure inasmuch as it described the actual life-history of a large number of individuals from birth to death. Whether, however, the life table death-rate is an absolute measure, that is to say, whether a district with a death-rate of 24 per 1,000 is 30 per cent. more unhealthy than a district with a death-rate of 18 per 1,000, has not been settled, an actual unit of ill-health not being yet established. The life table death-rate, however, has one property which places it as a measure above either the standardized death-rates or the crude death-rates, inasmuch as it has been found for England and Wales to be very closely connected with the density of population.
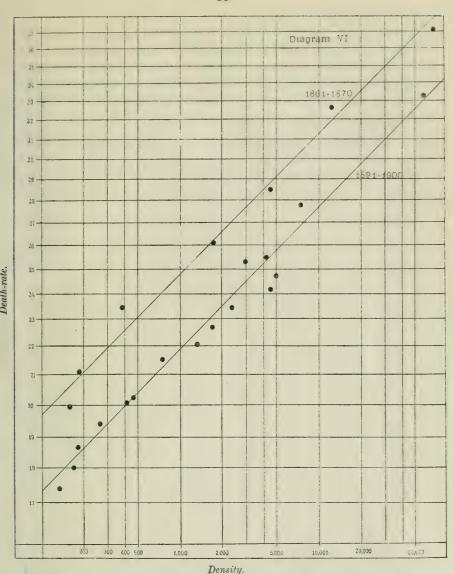
This subject was first considered statistically by the late Dr. Farr. His treatment of it is one of the brilliant attempts to extract the real meaning of figures so frequent in his work, but though this theory has not shared in the complete neglect that has been the lot of his attempt to put a quantitative measure to the course of epidemics, it has suffered as much from the kind of patronage with which it is usually discussed. On one at least of the great medical officers of health of his time, however—the late Dr. J. B. Russell of Glasgow—the theory exercised a strong fascination. My own copy of Farr's *Vital Statistics* came from Dr. Russell's library, and the whole passage referring to the law is lined with his characteristic nervous pencil marks, and in much of his work on vital statistics the influence can be easily traced.

The law itself, if the death-rate be denoted by D and the density of population (say the number of persons per square mile) by δ, is that

$$D = c\delta^m \ . \ . \ . \ (a)$$

where c and m are constants.

By Farr the crude death-rate was used and found to give a good measure of the facts. When later, the standardized death-rate being introduced, it seemed to be the proper course to adopt this measure the law obviously did not hold. Even with crude death-rates, its success as a descriptive formula was not nearly so marked. Thus in the absence of any *a priori* justification the law was relegated to a somewhat obscure position.

Density.

In this diagram the relationship of density to death-rate (Farr's Law) is shown for two epochs, 1861–1870 and 1891–1900. The ordinates are the logarithms of the life table death-rates, and the abscissae the logarithms of the number of persons living on each square mile. The observations are indicated by black circles and the theoretical straight line has been drawn for both cases. It will be observed that the two lines are parallel and that for each of the decades the observations group themselves very closely on the line.

Before proceeding to the justification of the law, however, it is necessary to have a clear idea of the kind of evidence necessary to establish it. The law must be a law of average, for on account of the arbitrary nature of persons living on an acre it is merely a rough approximation. The groups of localities which supply the figures must further be large, as some with better conditions will have higher

death-rates, and others with worse a lower. Nor can even a large city, with the exception possibly of London, be divided into small districts and these considered separately. A city population must be a whole population ; the slum is not wholly recruited from the slum by any means. A district consisting chiefly of persons engaged in trades and minor occupations may have a very high density and yet a low death-rate. All, or at least the great majority of the inhabitants, are respectable ; those who are not are driven elsewhere, yet the latter must be considered as part of the same population ; from this class some ascend in the social scale, but they do not constitute a separate population. It is obvious, therefore, that to obtain a suitable average a few groups only must be chosen. Dr. Farr made seven, Dr. Tatham sixteen ; the former may be too few, the latter seems too many. The effect of density is not merely as density. The country preserves life even in the presence of excess or dissipation : the town does not. Further, in the period of growth, children in the city do not get anything like the same chance as their fellows in the country, even though housing may be better and food more abundant. In addition, filth in the country is, at its worst, in most cases but a local nuisance, spreading enteric fever and diarrhoea at times, but not having the power of rendering a whole district foetid. All these influences act concurrently and cumulatively to depress health the more closely people are crowded together, and as life is a physico-chemical process this effect must be measurable, and should be capable of expression in some formula which goes back to chemistry and physics. Such a formula is that of Dr. Farr.

In order to illustrate the subject tables have been constructed, showing the figures used by Dr. Farr which refer to the decade 1861–1870. Dr. Farr used the crude death-rate. Fortunately, he also published the death-rates at each age period for the groups of populations on which he based his law. This allows standardized death-rates to be calculated in the manner which has hitherto been used, and from these standardized death-rates life table death-rates strictly comparable with the conditions of environment have been obtained by use of the equations already given (Table XII).

When the columns showing the results obtained by fitting the curve given by the equation at the beginning of this section (equation a) to the life table, crude and standardized death-rates are compared, it is seen that the crude death-rate fits less well than the life table death-rate, and that the standardized death-rates are very badly represented by the formula. The excellence of the fit of the life table death-rate to the formula is shown in Diagram VI. It will be noticed that the crude death-rate curve of Dr. Farr has an exponent of 0·1199. This value is much nearer the probable true exponent 0·100 than that found by Dr. Tatham to most nearly graduate the crude death-rates for the decade 1891-1900, namely 0·1276. This is explained by the fact that in the earlier period the crude death-rate was 22·42 as against a life table death-rate of 24·06, while in the later period the corresponding figures are 18·19 and 21·77. Dr. Farr had thus a better opportunity of formulating a law than his successors. Using the crude death-rate it became more and more difficult to accept the relationship demanded by the formula (Tables XVII and XVIII).

TABLE XVII. *Showing the figures relating to density and death-rate, 1861–1870.*

No. of Districts.	Density (persons per square mile).	Standardized death-rate. (1)	Do. fitted by least squares.	Crude death-rate. (2)	Do. fitted by Farr.	Life table death-rate. (3)	Do. fitted by least squares.
53	166	15·30	16·70	16·75	18·90	19·90	20·73
345	186	17·02	17·00	19·16	19·16	21·07	20·96
137	379	20·52	18·99	21·88	20·87	23·47	22·51
47	1,718	24·35	24·03	24·90	25·02	26·09	26·19
9	4,499	27·94	27·92	28·08	28·08	28·54	28·84
1	12,357	33·98	32·67	32·49	32·70 [1]	32·67	31·92
1	65,823	40·55	42·39	38·62	38·74	37·17	37·74
			E% =3·79		E% =2·70		E% =2·01
			Δ =1·17		Δ =0·90		Δ =0·61

(1) $R = 7 \cdot 534 \, D^{0 \cdot 15571}$ (2) $R = 10 \cdot 234 \, D^{0 \cdot 11898}$ (3) $R = 12 \cdot 419 \, D^{0 \cdot 10018}$

TABLE XVIII. *Showing the figures relating to density and death-rate, 1891–1900.*

1	2	3	4	5	6	7	8	9
No. of Districts.	No. of inhabitants divided by 1,000.	Density (persons per square mile).	Standardized death-rate.	Do. fitted by least squares. (1)	Crude death-rate.	Do. fitted by least squares. (2)	Life table death-rate.	Do. fitted by least squares. (3)
27	305	136	11·63	13·06	14·20	14·16	17·38	17·18
112	1,676	161	12·54	13·43	15·05	14·51	18·01	18·12
121	2,496	181	13·44	13·70	15·44	14·68	18·62	18·33
92	2,849	261	14·52	14·56	15·46	15 38	19·36	19·02
53	2,272	407	15·53	15·68	16·08	16·28	20·05	19·90
56	2,577	457	16·53	15·99	16·67	16·52	20·24	20·13
31	1,839	737	17·58	17·32	17·64	17·56	21·45	21·12
40	3,690	1,303	18·53	19·05	18·04	18·88	22·10	22·31
31	3,159	1,705	19·42	19·93	18·61	19·54	22·71	22·99
21	2,240	2,339	20·37	21·00	19·50	20·35	23·36	23·72
18	2,777	4,424	21·56	23·37	20·21	22·08	24·18	25·31
13	2,119	4,884	22·36	23·76	20·69	22·35	24·72	25·56
6	801	4,194	23·48	23·16	22·05	21·93	25·49	25·10
5	762	2,925	24·33	21·80	23·29	20·94	26·07	24·21
5	791	7,480	26·54	25·51	24·74	23·60	27·58	26·68
4	288	55,563	34·82	35·66	32·67	30·49	33·25	32·58
				E% =4·3		E% =3·8		E%₀ =2·03
				Δ =1·05		Δ =1·14		Δ =0·63

(1) $R = 12 \cdot 40 \, D^{0 \cdot 16715}$ (2) $R = 13 \cdot 57 \, D^{0 \cdot 12755}$ (3) $R = 10 \cdot 83 \, D^{0 \cdot 10078}$

NOTE.—Where E is the mean percentage error and Δ the square root of the mean of the squares of the actual errors, R the death rate and D the number of persons living per square mile.

After this full statement it is only necessary to detail the results obtained when life table death-rates have been taken as the measure of health. The formulae have been calculated for the four decades for which data exist, and the results are given in the accompanying table :

1861–1870	.	.	$D = 12 \cdot 42\delta^{0 \cdot 1001}$
1881–1890	.	.	$D = 11 \cdot 45\delta^{0 \cdot 0985}$
1891–1900	.	.	$D = 10 \cdot 83\delta^{0 \cdot 1008}$
1901–1910	.	.	$D = 9 \cdot 90\delta^{0 \cdot 1023}$

A misprint in the original of 37·7 has been corrected

Thus it is found that though the general health has improved, the power of the density has stood unchanged for forty years. That is to say, that the death-rate and density remained related in essentially the same way in the counties of England and Wales in 1905 as in 1865. It is the constant multiplier that has been affected by hygienic measures and not the law of the power. Hygiene acts surely all round but still is subjected to fundamental laws.

In correlating density and death-rate the stumbling-block has been London. Considering the density of the city the death-rate was nothing like so high as it should have been by Farr's law. The differences were really very great; for instance, in the decade 1861–1870 the formula as adjusted by myself gave a death-rate of 32 per 1,000 as against 26 per 1,000 actually found. The meaning of this exception was difficult to ascertain. In a former paper I ascribed it as probably due to the results of the extreme selection established by city life, as only those fitted to survive could hope to procreate children. While this might be expected to have such an effect, it was theorizing without proof. It was not possible to make any test of this matter till 1911. Prior to this the deaths occurring in institutions were not distributed to the registration districts to which they properly belonged, and some of the institutions, such as the London Hospital, were very large. In his annual report for London in 1911, however, Sir Shirley Murphy published standard death-rates for the different boroughs of London, for the five years 1907–1911, the deaths in institutions being ascribed to the districts to which they belonged. It was thus possible to calculate the life table death-rates for each borough.

The relationship between the density and the death-rate calculated for these life table death-rates has been found to be

$$D = 6 \cdot 33 \delta^{\,0 \cdot 1045}.$$

Here again we see that the relationship which has been found to hold for England and Wales holds also for London, the death-rate for each district in London being proportional to the tenth root of the density. The constant multiplier is, however, much smaller than that for England and Wales as a whole, showing that the discrepancy observed in the decade 1861–1870 still persists. London has thus achieved in some way or other a greater absolute healthiness than its density would suggest. This greater degree of health has not, however, absolved it from obedience to the general relationship between density and death-rate, the relation between the death-rates of different boroughs being determined by the general principle.

X. Fitting the Life Table Death-rates to the Formula $a(c-x)^{-n}$.

In Section VI some evidence was given as to the manner in which the death-rate varied after the age of 10 years. Taking the healthy districts as the standard, the mortalities in the more unhealthy districts and in cities were shown to vary so that the ratio of the death-rate in the more unhealthy districts to that of the healthy

TABLE XIX. *Showing the values of n, c, and log a obtained when fitting the expectations at 15, 45, and 75 to the formula $a(c-x)^{-n}$.*
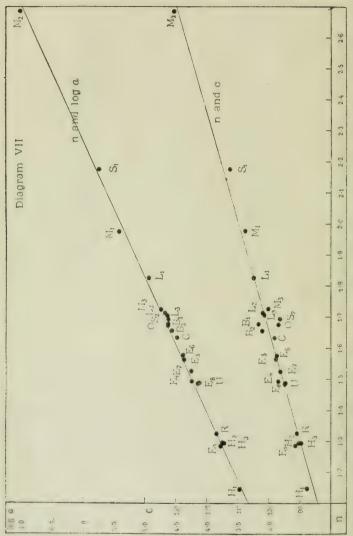
	n	c	$log\ a.$
E_3	1·285	91·4	3·783
E_4	1·493	96·9	4·217
E_5	1·566	97·6	4·352
E_6	1·576	97·6	4·366
E_7	1·525	96·1	4·235
E_8	1·485	94·7	4·138
H_1	1·147	87·6	4·051
H_2	1·295	90·1	3·769
H_3	1·294	89·6	3·782
B_1	1·677	103·2	4·611
B_2	1·657	102·0	4·556
M_1	1·976	107·5	5·300
M_2	2·684	130·6	7·013
M_3	1·724	100·0	4·715
L_1	1·826	104·7	4·930
L_2	1·711	101·9	4·654
L_3	1·705	101·2	4·631
S_1	2·176	112·4	5·727
S_2	1·691	96·1	4·600
O	1·673	96·7	4·601
C	1·632	98·0	4·468
U	1·488	94·6	4·139
R	1·325	90·8	3·779

districts was found to be the largest between the ages of 45–50 years. In other words, city life tells more against the middle ages than any other. In this section it is proposed to show that the reactions at each age period are very highly correlated.

The range of life in any locality between the ages of 10 years and 75 years, in view of the previous discussion, may be taken as sufficiently described by the life table death-rates. It is found that these death-rates can be graduated with great accuracy to the formula

$$D_x = a(c-x)^{-n},$$

where D is the life table death-rate at the age x and a, c, and n are constants. The necessary calculations have been made for most of the life tables referring to populations contained in the area of England and Wales, and the values of the constants are given in the accompanying table (Table XIX). It will be, perhaps, however, more intelligible to exhibit the relationship of the different constants diagrammatically. Explanatory diagrams have accordingly been constructed (Diagrams VII and VIII). It will be observed that the quantities c. n, and $log\ a$, taken pair by pair are so related that their values are in linear relationship. The correlation between each pair is singularly high, being in all cases over 0·97, so that given one of

Diagram VII

In this diagram the relationship found from twenty-three life tables between n and $\log a$ and n and c when the life table death-rates have been graduated to the formula $q(c-x)^{-n}$ is shown : it will be noted how closely the points group themselves on the straight lines, the chief divergence being found in tables based on small populations such as those for Brighton, Oldham, and Salford.
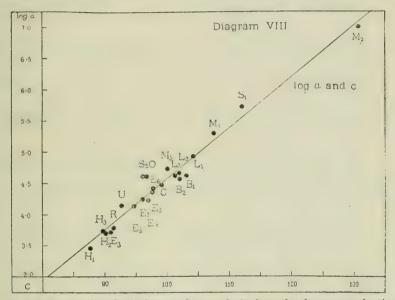
the constants the other two are practically determined. The relation-
ships between each pair are given by the equations,

$$log\ a = \cdot07751\ c - 3\cdot149$$
$$n = \cdot44393\ log\ a - \cdot380$$
$$n = \cdot03523\ c - 1\cdot860.$$

The reaction of life to environment is thus very rigidly limited, and
though in one place or another there may be small deviations, yet
the deviation in no place can be very great. The larger deviations,
however, to be observed in the diagrams are in general, though not
always, most evident in those cases in which the life table refers to

In this diagram the relation between log a and c is shown for the same graduation.
It will be noted again that the divergence chiefly occurs in the same life tables
referring to small districts.

a small number of persons. Considering the character of the in-
habitants of towns such as Salford or Brighton, though the deviations
may be real, it is more likely they are due to the error of small
numbers. Even if such slight differences occur it seems no less true
that a fundamental relationship of environment to life table death-
rates exists.

XI. COMPARISON OF LIFE AS FOUND IN VARIOUS LIFE TABLES.

It is intended in the next section to give some consideration to life
tables as a guide to the use of death-rates. The whole columns con-
tained in a life table are not of equal importance for this purpose. I
have therefore made a selection from the tables to show the important
facts ascertained for a wide range of environment and for different
epochs. Further, in Part II I give some notes on the theory of life
tables and also directions for the rapid calculation of those parts of
a life table useful for the discussion of health problems.

TABLE XX a. Giving the number of survivors at each age out of 100,000 born in England and Wales at different periods, and for some of the healthy and unhealthy districts.

MALES.

Age.	H_1	H_2	H_3	E_3	E_4	E_5	E_6	E_7	E_x	B_2	S_1	M_1	M_2	M_3	L_1	L_2	L_3	C.B.	U.	R.
0	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000
5	84556	85617	86120	72572	73407	73149	75028	79398	82627	75590	62092	67897	62326	70114	71898	77792	98630	98408	98517	98780
10	80524	84006	83628	68586	70899	72348	73130	78092	81211	74550	60296	64676	59323	68361	70152	76472	96908	96423	96763	97064
15	78440	82927	81221	67278	69612	72619	72537	77296	80464	73785	59102	63076	57540	66656	69296	75711	94770	94126	94818	95176
20	76138	81313	78284	64434	68403	69381	71171	76112	79343	72130	57979	61644	55646	65016	68072	74634	91909	91230	92562	93030
25	73142	78503	76325	62122	65708	68965	69389	74546	77869	70651	56013	59645	52924	63220	66555	73230	88052	87484	88930	90552
30	70036	74933	73235	59509	63004	60192	67820	72710	76292	68852	53878	56824	49099	60842	64602	71482	83025	82757	86102	87494
35	66895	74313	71231	56111	59886	56144	64817	70172	74219	65732	51553	53774	44315	57765	61742	69131	76690	76651	81328	83714
40	63720	68651	68686	53166	56348	51764	61596	67648	71672	62373	48340	48753	38996	53816	57941	65948	68921	68970	74505	78768
45	60502	65406	62674	49577	52237	46298	57701	64230	68459	58360	43491	43665	33319	49133	53471	61904	59426	59324	66489	72024
50	57138	61400	58159	45573	47698	39840	53969	59903	64833	53284	38081	38031	27095	43318	48272	56923	46315	47783	55551	62872
55	53512	56264	60923	40946	42468	33221	47385	54439	59012	47535	32117	31859	20480	38318	42224	50925	36233	35071	42604	51043
60	49226	49107	53197	35633	36501	25863	40852	47563	52110	41041	25206	25116	14945	30308	35325	43872	23432	21495	27838	36146
65	44003	40425	47777	29459	29716	18589	33231	39278	43523	33836	17895	18068	10117	23111	27764	35680	12286	10737	14918	20810
70	35055	29010	38886	22349	22206	13389	24463	29898	33430	25808	11594	11423	6028	15015	19828	26626	4815	4065	6177	8801
75	25561	17088	26732	14808	14496	8002	15861	19753	22424	17655	6064	6069	2906	8327	12199	17449	1349	1048	1678	2417
80	15800	7912	14349	8034	7735	2987	8230	10607	12193	9835	2428	2563	1087	3688	6038	9377				
85	7102	2976	6008	3298	3079	697	3132	4348	4957	4012	1118	804	323	1162	2217	3721				
90	2536		1488	932	802		772	1116	1260	745	212	173	77	219	551	937				

FEMALES.

Age.	H_1	H_2	H_3	E_3	E_4	E_5	E_6	E_7	E_x	B_2	S_1	M_1	M_2	M_3	L_1	L_2	L_3	C.B.	U.	R.
0	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000	100000
5	85556	85617	86120	75655	76262	78324	78214	82178	85605	78656	65867	71791	66323	74163	78615	80479	98828	98542	98694	98671
10	80524	84006	83795	71577	73838	76615	76572	80755	83598	77273	63909	68257	62873	71738	76636	79107	97546	96871	97219	97063
15	78400	82927	82324	69692	72496	75006	75550	79808	82774	76273	62880	66614	61115	70105	75493	78305	95965	94998	95528	95254
20	76136	81313	80428	67412	70795	74432	74177	78755	81681	75307	61681	65219	59341	68610	74579	77370	93935	92713	93522	93156
25	73142	78503	78756	64434	68486	72179	72539	77300	80412	74274	60179	63299	56857	66803	73306	76312	91106	89644	91046	90804
30	70036	74933	74680	61277	65842	70005	70582	75578	78953	72899	58337	60647	53597	64380	71631	74991	87390	85949	88012	88160
35	66895	74313	74360	57991	62884	67099	68215	73749	77183	71044	55736	57336	49673	61309	69181	73135	82612	81145	84043	84952
40	63729	68651	71744	54584	59611	63401	65301	71306	74998	68584	52380	53512	45122	57783	65914	70571	76752	75100	78935	80602
45	60502	65406	68690	51010	56017	60101	61918	68359	72283	65450	48211	49192	39962	53873	62102	67407	69282	67200		74597
50	57138	61400	64637	47325	52690	56430	58032	64742	68880	61619	43487	44197	34301	49279	57602	63487	60136	57288	62731	66484
55	53512	56264	59535	43353	47744	51638	53311	60179	64177	56984	37840	38324	28164	43691	52163	58591	48065	45299	51462	54690
60	49226	49107	52463	38307	42284	45768	47301	54157	58659	51472	30997	31544	21596	36963	45635	52563	35290	30773	36446	41838
65	43003	40425	43019	32417	36117	38850	39830	46716	51187	44766	23473	24027	15006	29108	37948	45106	19755	17277	21636	26103
70	35076	29010	31204	25316	27723	29922	30617	37615	41887	36002	16075	16323	9474	20383	29066	36034	9755	7382	9911	12616
75	25661	17088	18601	17480	19057	20421	21069	26418	30690	25837	8786	9459	5275	11895	19565	25724	3033	2258	3262	4152
80	15800	7912	8381	10039	10894	11454	11807	15544	18086	15176	3961	4468	2548	5640	10725	15387				
85	7002	2976	2429	4442	4763	4833	4993	7063	8324	6439	1707	1653	1029	2037	4443	7010				
90	2536			1380	1423	1342	1433	2158	2704	1517	449	463	329	540	1252	2123				

TABLE XX b. *Showing the expectation of life in England and Wales at different periods, and for some of the healthy and unhealthy districts.*

MALES.

Age	H_1	H_2	H_3	E_3	E_4	E_5	E_6	E_7	E_8	B_2	S_1	M_1	M_2	M_3	L_1	L_2	L_3	C.B.	U.	R.
0	48.56	51.48	52.87	39.91	41.35	43.66	44.13	48.53	51.50	44.92	33.30	34.71	28.78	38.11	40.98	46.74				
5	54.39	57.05	58.26	49.71	50.87	52.75	53.50	55.90	57.14	53.94	48.02	45.59	40.53	48.65	51.60	54.82				
10	51.28	53.03	54.16	47.05	47.60	49.00	49.63	51.81	53.08	49.80	44.39	42.75	37.47	45.03	47.84	50.73				
15	47.20	48.62	49.67	43.18	43.41	44.47	45.21	47.31	48.57	45.29	40.00	38.78	33.56	41.12	43.40	46.21	46.74	46.28	49.01	51.45
20	43.40	44.41	45.37	39.48	39.40	40.27	41.02	43.01	44.21	41.09	35.93	34.62	29.61	37.08	39.13	41.84	42.35	41.99	44.71	47.08
25	39.93	40.39	41.32	36.12	35.48	36.28	37.01	38.86	40.00	37.12	32.10	30.69	26.00	33.08	34.96	37.59	38.06	37.80	40.48	42.84
30	36.45	36.52	37.32	32.76	32.10	32.52	33.07	34.76	35.81	33.23	28.28	27.08	22.82	29.26	30.94	33.45	33.87	33.66	36.25	38.64
35	32.90	32.70	33.32	29.40	28.64	28.91	29.24	30.79	31.71	29.45	24.44	23.76	20.01	25.69	27.25	29.50	29.84	29.65	32.07	34.47
40	29.29	29.19	29.37	26.06	25.30	25.42	25.64	27.16	27.74	25.90	20.87	20.68	17.39	22.38	23.87	25.80	26.03	25.80	28.02	30.35
45	25.65	25.19	25.19	22.76	22.07	22.06	22.20	23.27	23.92	22.54	17.92	17.80	14.93	19.27	20.65	22.31	22.45	22.13	24.07	26.31
50	22.03	21.53	21.74	19.54	18.93	18.82	18.90	19.76	20.29	19.41	15.13	15.06	12.77	16.21	17.60	19.04	19.00	18.69	20.33	22.39
55	18.49	18.00	18.12	16.45	15.95	15.71	15.79	16.48	16.89	16.14	12.45	12.49	10.96	13.25	14.76	15.98	15.95	15.48	16.85	18.63
60	15.06	14.66	14.72	13.53	13.14	12.88	12.93	13.49	13.78	13.45	10.16	10.16	9.24	10.63	12.14	13.14	13.09	12.57	13.66	15.13
65	12.00	11.60	11.61	10.82	10.55	10.31	10.34	10.80	10.99	11.01	8.30	8.15	7.48	8.50	9.76	10.56	10.51	9.99	10.84	11.95
70	9.37	8.88	8.45	8.45	8.27	8.04	8.05	8.39	8.53	8.66	6.51	6.48	5.91	6.77	7.66	8.30	8.17	7.49	8.35	9.11
75	7.15	6.56	6.56	6.49	6.34	6.10	6.15	6.41	6.49	6.49	5.19	5.11	4.74	5.28	5.91	6.35	6.28	5.99	6.45	6.81
80	5.37	4.70	4.78	4.93	4.79	4.52	4.62	4.86	4.90	4.63	4.89	4.02	3.98	4.02	4.53	4.75	4.79	4.64	4.96	5.01
85	4.00	3.30	3.45	3.73	3.56	3.29	3.45	3.53	3.72	3.01	3.04	3.16	3.45	2.98	3.48	3.48	3.71	3.55	3.72	3.67
90	2.99	2.31	2.50	2.84	2.66	2.37	2.58	2.56	2.87	2.06	1.79	2.48	2.94	2.16	2.69	2.52	2.75	2.71	2.98	2.66

FEMALES.

Age	H_1	H_2	H_3	E_3	E_4	E_5	E_6	E_7	E_8	B_2	S_1	M_1	M_2	M_3	L_1	L_2	L_3	C.B.	U.	R.
0	49.45	54.04	55.71	41.85	44.62	47.18	47.77	52.38	55.35	50.19	36.81	38.44	32.67	41.58	45.33	51.41				
5	53.93	58.01	59.53	50.33	53.06	54.92	55.79	58.53	59.94	58.52	50.31	48.06	43.46	50.64	55.12	58.63				
10	50.88	54.01	55.46	47.67	49.76	51.10	51.97	54.53	55.91	54.53	46.79	45.43	40.94	47.28	51.49	54.61				
15	47.04	49.68	51.06	43.90	45.63	46.55	47.61	50.08	51.14	50.21	42.51	41.50	37.05	43.32	47.10	50.14	51.13	49.64	51.76	53.08
20	43.50	45.62	46.93	40.29	41.66	42.42	43.44	45.77	47.10	45.82	38.29	37.33	33.08	39.21	42.77	45.72	46.73	45.34	47.41	48.76
25	40.17	41.71	42.86	37.04	37.98	38.50	39.37	41.54	42.80	41.42	34.18	33.38	29.41	35.20	38.46	41.32	42.29	41.48	43.09	44.52
30	36.85	37.91	38.82	33.59	34.41	34.76	35.39	37.36	38.54	37.15	30.18	29.73	26.04	31.43	34.30	37.00	37.71	36.84	38.81	40.32
35	33.46	34.16	34.79	30.59	30.90	31.16	31.52	33.31	34.37	33.06	26.47	26.30	22.90	27.87	30.42	32.87	33.71	32.68	34.58	36.17
40	30.00	30.38	30.81	27.34	27.46	27.60	27.82	29.37	30.30	29.15	23.00	22.99	19.95	24.42	26.80	28.97	29.67	28.71	30.45	32.04
45	26.16	26.56	26.84	24.06	24.06	24.05	24.20	25.42	26.31	25.42	19.75	19.79	17.20	21.01	23.29	25.21	25.82	24.81	26.11	27.93
50	22.87	22.75	22.92	20.75	20.68	20.56	20.61	21.81	22.51	21.84	16.63	16.71	14.82	17.72	19.91	21.40	22.17	21.15	22.54	23.88
55	19.21	19.06	19.12	17.43	17.33	17.23	17.21	18.27	18.87	18.11	13.73	13.91	12.25	14.67	16.72	18.19	18.66	17.64	18.83	20.03
60	15.49	15.56	15.59	14.31	14.21	14.10	14.10	14.99	15.48	15.10	11.19	11.35	10.31	11.87	13.74	14.98	15.39	14.11	15.39	16.43
65	12.58	12.36	12.36	11.51	11.42	11.26	11.27	11.99	12.36	11.98	8.98	9.11	8.54	9.38	11.01	12.03	12.34	11.16	12.28	13.07
70	9.85	9.53	9.48	9.02	8.95	8.77	8.78	9.25	9.58	9.26	6.97	7.25	7.18	7.31	8.59	9.42	9.57	8.80	9.30	10.04
75	7.52	7.11	7.10	6.93	6.87	6.48	6.70	7.10	7.29	6.91	5.49	5.76	6.03	5.72	6.57	7.17	7.29	6.77	7.21	7.58
80	5.61	5.23	5.24	5.36	5.20	5.00	5.05	5.36	5.49	4.87	5.09	4.62	5.02	4.53	4.97	5.34	5.39	5.16	5.47	5.45
85	4.19	3.77	3.83	3.98	3.88	3.71	3.80	3.91	4.19	3.36	3.40	3.76	4.13	3.61	3.75	3.90	4.02	3.98	4.16	4.15
90	3.11	2.71	2.80	3.01	2.90	2.75	2.87	2.94	3.16	2.34	2.85	3.11	3.34	2.96	2.84	2.82	3.10	3.10	3.18	3.06

TABLE XX c. *Showing the population living in each age group of five years in England and Wales at different periods, and for some of the healthy and unhealthy districts.*

MALES.

Age.	H₁	H₂	H₃	H	E₃	E₄	E₅	E₆	E₇	E₈	B₂	S₁	M₁	M₂	M₃	L₁	L₂	L₃	C.B.	U.	R.
0	88172	85367	81573	81079	98569	90925	92015	90100	85459	83175	89523	104694	108236	122117	101699	94770	87714	106260	107214	101298	96603
5	82118	79462	78107	78324	89354	86922	84773	83866	80978	78554	83608	91640	95178	105383	98654	86384	82361	104407	105270	99630	95163
10	80215	78444	77265	77254	85974	85038	83398	82710	80059	78512	82594	89863	91929	101466	98554	85086	81413	102557	102908	97745	93432
15	78421	77393	76286	76028	82068	83154	82450	81457	79057	77617	81468	88245	89867	98406	86408	83825	80444	99913	100187	95623	91475
20	75673	75546	74902	74333	79934	81091	80569	79546	77628	76829	79639	85591	87441	94463	81473	80063	79109	97173	96614	93021	89242
25	73086	73670	73118	72307	76464	77880	78103	77464	75896	74829	77364	82503	83984	88788	77912	77173	77431	91600	92061	89741	80566
30	70228	71450	71315	69987	72679	74315	74991	74910	73812	73074	74709	79187	79319	81260	73295	73087	75272	85540	86236	85526	83263
35	67172	68075	68510	67483	69011	70264	71313	71080	71203	70872	71392	75250	73496	72421	67599	68019	72319		78814	79842	79067
40	64106	64071	66518	64862	64428	65712	67012	67630	68004	68093	67231	69042	66630	62885	61155	62142	68456			72323	73442
45	60813	62730	63511	62002	59603	61347	62021	62837	64025	64546	62175	61224	55896	52566	54127	55286	63637	68795	69481	62425	65745
50	56821	58757	59757	58741	54356	54548	56230	57113	59003	59993	56205	52713	41086	41464	45835	47384	57770	57727	57978	50253	55002
55	52455	53651	55633	54546	47970	47822	49424	50272	52662	54079	49379	43187	31091	30818	35774	38534	50792	45314	44890	35948	42549
60	46776	47598	48879	49034	40934	40174	41373	42103	44836	47554	41758	32258	12382	21660	24922	29046	43649	31882	30463	21522	27583
65	38831	39630	40879	41726	32517	31405	32176	32803	35725	37467	33238	21933	5972	13921	15118	19453	33377	18663	17072	10408	13988
70	29634	29944	30859	32432	23239	22186	22438	22922	25585	27143	24198	13221	2238	7593	7653	10923	23537	8763	7631	3667	5032
75	19460	19216	19626	21756	14156	13266	13230	13408	15454	16652	15285	5885	608	3288	2977	4794	14192	3031	2504	1022	1248
80	10382	10332	9608	11593	6419	6310	6034	6171	7448	8032	7551	2543	124	1116	785	1519	7653	794	613		
85	4049	3971	3220	4382	2419	2135	1881	1998	2577	2819	2344	907		307	125	362	2977				
90 & upwards	1236	586	703	1141	663	516	369	451	589	758	342	114		78			785				
Total population	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000

FEMALES.

Age.	H₁	H₂	H₃	H	E₃	E₄	E₅	E₆	E₇	E₈	B₂	S₁	M₁	M₂	M₃	L₁	L₂	L₃	C.B.	U.	R.
0	88741	81079	79717	79446	97367	92786	88207	86664	81748	79446	82673	99791	102434	113456	96740	88883	82236	97224	100010	95994	93303
5	82733	78324	76592	77056	87322	83776	81926	80793	77629	76056	77607	87954	90763	98445	87605	81365	77473	96030	98427	94646	92206
10	80452	77254	75450	75157	84253	82068	80882	79604	76690	75157	76501	86088	87628	94750	85242	80085	76555	94643	98649	93123	90599
15	78806	76028	74562	74299	82067	78042	79099	78390	75740	73228	75518	84604	85772	92190	83412	79005	75510	92540	94586	91349	88761
20	75610	74333	73137	73228	75235	75185	77779	76802	74539	73228	74542	82787	83682	88967	81463	77762	74748	96030	91895	89191	86664
25	73252	72307	71536	72002	71166	72279	72629	74927	73127	72002	73363	80530	80690	85182	75624	76236	73602	90540	88463	86549	84320
30	68266	69987	69777	70653	67292	68022	69397	69923	71407	70653	71703	77534	76793	79056	71637	71077	72089	87350	84229	83187	81598
35	66014	67483	67813	68707	63155	64803	65864	66605	69275	68707	69619	73494	72141	72577	67176	67336	69934	83200	78813	78836	78084
40	62589	64882	65581	66564	58788	60634	61985	62830	66702	64564	64838	68426	64854	65142	62107	67336	67143	78025	71828	73077	73232
45	59482	62002	63069	63821	54170	55898	57329	58351	63583	60326	63371	62360	60821	50852	55989	62997	63721	71532	84229	83300	81598
50	55435	58741	59900	60326	48908	55989	51801	58351	59715	55732	59164	55330	53762	47834	55989	57786	59447	63414	71828	78836	78084
55	52132	54546	55952	55732	42412	50489	44777	52784	54682	55732	54114	46884	45525	38089	48588	51507	54147	53549	68213	73077	73232
60	46590	49034	49010	49743	34692	43786	43776	45714	48250	49743	48075	46833	36186	28005	39834	44038	47023	41314	62848	65219	66700
65	38672	41726	44010	40436	25619	35550	36363	37140	40436	40436	40415	29797	36198	18639	29802	35321	39577	27675	51893	55425	58090
70	30803	32432	33451	32522	25619	26246	26707	27232	30662	32522	30862	16867	10596	11092	19351	25541	30096	14940	38386	42626	64356
75	20634	21756	22303	21718	16328	16646	16774	17073	19909	21718	20558	8100	8805	5814	10345	15747	19922	5826	24000	27921	31975
80	11618	11593	11790	11646	8393	8554	8354	8526	10567	11646	10701	3901	3754	2610	4364	7712	10461	1841	12035	14886	17937
85	4846	4382	4170	4717	3232	3217	3002	3105	4126	4717	3608	1229	1241	963	1399	2755	4153		4508	5967	7469
90 & upwards	1505	1141	1221	1576	993	925	782	862	1212	1576	706	347	375	337	384	747	1163		1410	2005	2397
Total population	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000	1000000

XII. Effect of Environment on Length of Life.

A case which has hitherto not been considered now presents itself. The expectation of life is well known. There is, however, a different aspect of expectation. If a person living in an unhealthy environment die at an early age, how much longer would he have lived had he been able to live in a healthy environment ? Before proceeding to inquire into this, I wish to make a few remarks on the use of the word ' age '. The phrase ' high age ' is often used confusedly in common parlance, the degree of physical weakening due to advance in life, and the number of years lived being imperfectly distinguished. To save this ambiguity, ' high age ' will imply the number of years lived, ' old age ' will imply the physical state of the persons involved. Thus, I am going to postulate as a general principle that though there are a great many more persons living at higher ages in the country than in the town, the number of ' old aged ' persons is the same in both places. This implies that life in the environment of the town brings about senility of the tissues at an earlier age than life in a rural district. If this be not granted then, the succeeding argument must not be taken as proved.

It is not apparently possible by any means at our disposal to make an exact estimate of this ageing process. It can, however, be illustrated graphically (Diagram IX), and I think the approximation obtained by this graphical representation is sufficiently close for the purpose of argument ; even though the error be 15 to 20 per cent., the argument remains essentially the same. A comparison is made between the data given in the life tables for the decade 1891–1900 for England and Wales as a whole and for the healthy districts. The age groups are five yearly groups, beginning at the age of 9 years, as at that age the death-rate in England and Wales as a whole and in the healthy districts of England and Wales is identical ; so that a person brought up in a town to the age of 9 years and then transferred to the country will have no immediate benefit for the change. This test is rough but sufficient.

In the diagram in the lower part each rectangle gives the number of deaths which occur at each five yearly period of life from 9 years and upwards for England and Wales as a whole. The mean age at which such groups of persons die is assumed to lie half-way along the rectangle ; the approximation is sufficiently accurate.

To compare this graph with the graph of the healthy district life table requires a new postulate. This postulate is, that persons dying at any specific age are, taking a considerable average, likely to be a group. Thus persons dying between the ages of 10 and 15 years in the town are likely to die at approximately the same age in the country—the death-rates being essentially the same at these ages : further, persons dying, say, between the age of 50 and 55 years in the town would, on the whole, assuming these to be a group, had they lived in the country, lived six or seven years longer. The graph in the upper part of the diagram, based on the healthy districts for the years 1891–1900, has been constructed on this assumption. The groups of

D
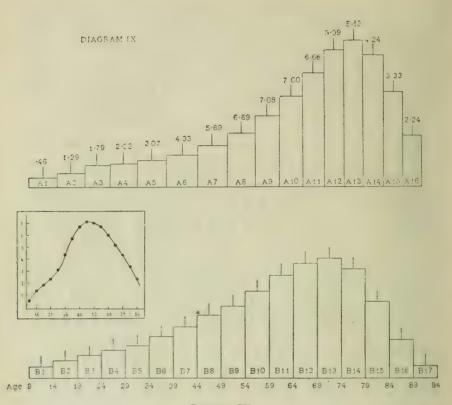
DIAGRAM IX.

In the lower part of this diagram a graph is shown of the number of deaths which occur in each 5 years of age, commencing with 9 years in the life table for England and Wales, 1891–1900, the greatest number occurring between 69 and 74 years. In the upper part of the diagram the deaths occurring in the healthy districts of England are similarly graphed, not, however, in five yearly periods. Each block in the upper diagram corresponds to each block in the lower, this distribution being made on the assumption that persons dying about a certain age form a group, which group may live somewhat longer in the country as a group but will not have their standard deviation greatly altered. It will be observed that in the first part of this graph the bases of each block are longer than in the lower graphs and that this persists until the age of 50 years when the base line of each block becomes smaller, the result being that a like number of deaths has occurred in 5 years in the lower graph and 4 years in the upper. Taking the mean of each block as the average age at death, the differences in length of life are shown by the figures above the blocks in the upper part of the diagram, the maximum increase of life occurring about 50 years. These figures are graphed in an inset between the diagrams to illustrate the manner in which they vary.

deaths which are considered to correspond are marked by numerals. Thus the number of deaths in Block A 1 cover a period of nearly a year longer in the healthy districts and correspond to Block B1. In the same way, the number of deaths in Block A 11 are equivalent to those in Block B 11. The process is continued to the end of life. It is found that for a considerable time the blocks of equal area have much larger bases in diagram A than in diagram B. About the age of 60 years the bases of the two become approximately equal. After this epoch, however, the bases become much narrower ; when Block A is compared with Block B at these ages the same number of deaths occur in a very much shorter time. This relation holds until the end of life.

On the assumption then that each of these blocks of persons correspond, the difference of age at which the same person would die in the two environments corresponds roughly with the difference between the curves placed at the middle point of the rectangle in the diagram. Thus, persons dying at the age of 51 years in the average environment would have, had they lived in the country, a mean life of seven years longer. This is the maximum difference. At higher ages the difference is less. The person who has the potentiality of living to the age of 80 years has a force of life which is more or less independent of environment. His system can stand the ' whips and scorns of time '. It is on the person who is likely to die at the age of 50 to 55 years that the storm of life is most likely to have the effect of producing premature senility.

To supplement this it would be natural to use the life tables constructed by Mr. King for the years 1910–12 which differentiate the rural, urban, and county borough areas of England and Wales more perfectly than the life tables just used. Unfortunately Mr. King does not begin these life tables until the age of 15 years. The start is then later than the period of equal death-rates. The process just shown has, however, been applied to Mr. King's tables and with the same result. The difference between the rural areas and the county boroughs are very much the same as that between the two life tables for the decade 1891–1900, while the data referring to urban districts fall between.

XIII. Phthisis.

' The consumption a flattering disease cozening men into hope of long life at the last gasp.'

Up to the present the discussion of the matter at issue has been general. It is now necessary to proceed to the particular. The disease phthisis offers one of the best tests of the validity of rough comparisons. It is selected because it is still the battle-ground of the clinical statisticians. Every medical journal contains pages in which crude death-rates from phthisis calculated against the whole population are offered for purposes of comparison. I think it is fair to remark that on whatever theory the prevalence of phthisis at
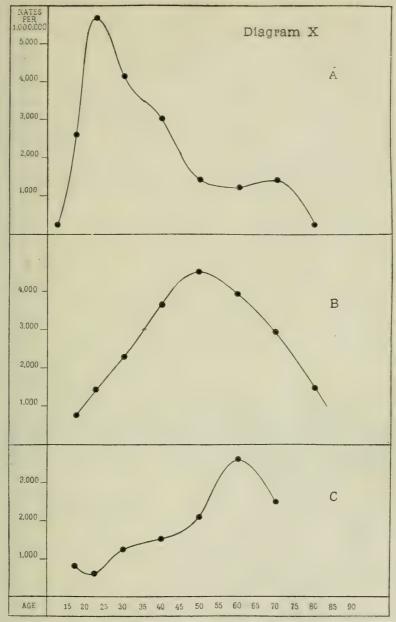
different ages and in different environments is to be explained such comparisons are of little value. Consider, for instance, the age distribution of the death-rates among males from phthisis in Shetland, in London, and among ironstone miners. These are shown in the accompanying diagram (Diagram X). It is obvious at a glance that the greatest death-rate in Shetland is between the ages of 20 and 25 years : in London between the ages of 45 and 55 : among ironstone miners between 55 and 65 years. How the understanding of such phenomena is helped by expressing death-rate differences by any single unit passes my comprehension. Poincaré has remarked that mathematics are sometimes a nuisance : the epigram may certainly be justly applied to such statistical methods.

But the matter goes much deeper than figures. The phthisis deathrates in the young adult are distributed and react to environment in complete contrast to the death-rates due to phthisis in middle age. The former tends to be a disease of rural districts, the latter one of the towns. Further, as far as present evidence goes, bad feeding, sitting in wet clothing, and such-like causes are the predisposing elements in young adult phthisis. On the other hand, middle age phthisis is associated with depression of health due to industrialism. I have made elsewhere an attempt to distinguish statistically what I think different types of phthisis, namely, those of youth, middle age, and old age. The method is given in Section XXVII.

As these differences undoubtedly exist, it becomes essential to inquire what are the probable proportions of each of these conditions. The age periods at which phthisis causes death are shown sufficiently in Diagram X opposite. In previous papers I have given a method of estimating the amount of phthisis which may be assumed due to special age periods. The results of applying this analysis to certain districts are shown in Diagrams XI and XII. In these the actual death-rates are shown by solid black circles, the death-rates due to each component by thin lines, and the theoretical complete death-rate, the sum of the components at each age period, by a continuous heavy line. It will be observed that in districts of very various life conditions the analysis holds. In North Wales the chief amount of phthisis among males is in early adult life and in old age. In South Wales the same holds among females except that phthisis among them is much more uncommon in old age. Essex, on the other hand, may be taken as a type of county in which the amount of phthisis among young adult and elderly persons is small, the bulk of the deaths occurring in middle age. The method of analysis is given in an improved form in Section XXVII. As now offered it permits the direct calculation of the standardized deathrates from each type of phthisis in any district.
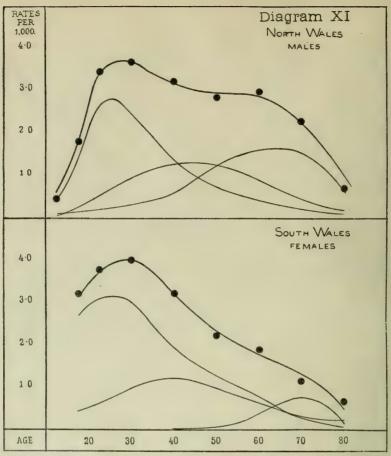
The question as to whether the death-rate can be split up in this manner is one which of course demands a good deal of justification. But the diagrams show how the phenomena in different places and districts can vary. The separation appears therefore essential. One kind of condition, namely a life in rural environment, is observed to be associated with death from phthisis at young adult ages ; another responding to environmental conditions such as those in

RATES
PER
1,000,000

Diagram X

5,000

4,000

A

3,000

2,000

1,000

AGE

4,000

B

3,000

2,000

1,000

3,000

C

2,000

1,000

15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
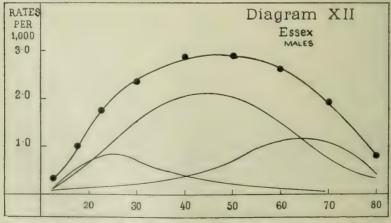
PHTHISIS.—In this diagram the death-rates per million from phthisis are shown in three types of case for age periods 15 years and upwards.

Diagram (A) refers to males in Shetland 1881–1900 ; (B) to males in London 1901–1910 ; and (C) to ironstone miners 1900–1902. The great difference of the age at which the chief number of deaths occur is easily seen.

RATES
PER
1,000.

4·0

3·0

2 0

1 0

Diagram XI

NORTH WALES

MALES

SOUTH WALES

FEMALES

4·0

3·0

2·0

1 0

AGE   20   30   40   50   60   70   80

PHTHISIS.—This diagram shows the analysis of the phthisis death-rate to the three types for males in North Wales and for females in South Wales. The finer lines represent the three components, the heavy line the sum of the three, and the black circles the actual observations. It will be observed in both of these that the type of phthisis in early life predominates.

RATES
PER
1,000

3·0

2·0

1·0

Diagram XII

Essex

MALES

20   30   40   50   60   70   80

PHTHISIS.—This diagram shows the same analysis for phthisis among males in Essex. In this case much the greatest amount of phthisis is at middle age.

urban districts tends to produce death from phthisis in middle age ;
a third kind of response among miners of all kinds—coal, iron, tin,
lead, slate, produces phthisis in old age. It does not seem right to
combine the types found in different parts of a county and to speak
of county death-rates as a whole as a measure of any importance
if two or three different responses to environment can be separated.
That the analysis has a sufficient basis is shown by the high correla-
tions which obtain between the amounts of each type of phthisis in the
two sexes ascertained when the analysis for both sexes is made for
each county. This high correlation is in face of the fact that the age
distribution of deaths from the three types varies considerably
between males and females. Thus between the amounts of young
adult phthisis in the two sexes the correlation is 0·79, of middle
age 0·76, and of old age 0·60 respectively. The first two corre-
lations must be considered as specially high when, in addition to
the fact that the method of analysis is purely tentative, account is
taken of the different environmental and industrial conditions of
the sexes in the several counties. In some cases males, in others
females, have the best working surroundings. Further, that the
correlation in the amounts of old age phthisis is as high as 0·60 lends
strong support to the theory that the analysis into the three types
has some physiological reason. Phthisis in old age is very uncommon
in females, being at most only one-fourth of the amount experienced
by males, yet when an analysis which is built on approximation
and which must have a large experimental error is used for the
calculations, the correlation is still very marked. This suggests
that the features revealed by the analysis are in the nature of
things.

To return to the question of absolute measure as suggested at
the end of Section VII, it is quite obvious in the case of phthisis
in all its different types that the standardized death-rates are for
nearly all purposes equivalent to life table death-rates. In the
accompanying table (Table XXI) an analysis of the phthisis death-
rates for England and Wales has been made for the five decades for
which corresponding life tables exist. It is possible thus from each
standardized death-rate to calculate the corresponding life table
death-rates for each type of phthisis by applying the death-rates
calculated for each age group to the standard population. The
figures are given for both males and females. It is to be noted that
the progression from large to small death-rates in both cases is
practically identical. The correlations are in all cases unity. For
ordinary statistical purposes, therefore, it is quite sufficient to take
the standardized death-rates for each type of phthisis as derived
from the analysis.

It must, in conclusion, be definitely posited that the lumping
together of the whole phthisis deaths independently of their age
grouping is in the present state of knowledge unjustifiable.

TABLE XXI. *Showing the standard death-rates and the life table death-rates for each type of phthisis among males at ten years and upwards, and females at fifteen years and upwards, in England and Wales, 1851–1910.*

MALES

Date.	'Young Adult' Type.		'Middle Age' Type.		'Old Age' Type.	
	Standard death-rate.	Life table death-rate.	Standard death-rate.	Life table death-rate.	Standard death-rate.	Life table death-rate.
1851–1861 . .	1·52	1·40	1·12	1·20	0·49	0·61
1871–1880 . .	0·88	0·81	1·71	1·84	0·24	0·29
1881–1890 . .	0·55	0·51	1·58	1·72	0·24	0·30
1891–1900 . .	0·32	0·30	1·45	1·59	0·21	0·26
1901–1910 . .	0·24	0·21	1·16	1·27	0·26	0·33
	$r = 1·000$		$r = 0·999$		$r = 1·000$	

FEMALES

Date.						
1851–1861 . .	2·14	1·93	1·42	1·41	0·124	0·178
1871–1880 . .	1·38	1·24	1·36	1·35	0·068	0·098
1881–1890 . .	0·93	0·82	1·22	1·19	0·065	0·096
1891–1900 . .	0·52	0·45	1·05	1·03	0·058	0·087
1901–1910 . .	0·41	0·35	0·79	0·76	0·064	0·102
	$r = 1·000$		$r = 1·000$		$r = 0·995$	

Equations connecting the life table and the standard death-rates.

	Males.	Females.
'Young Adult' type . . .	$y = 0·9233x + 0·004$	$y = 0·9144x - 0·028$
'Middle Age' type . . .	$y = 1·0798x + 0·008$	$y = 1·0296x - 0·055$
'Old Age' type	$y = 1·2505x - 0·002$	$y = 1·3615x + 0·085$

where y denotes the life table death-rate, and x denotes the standardized death-rate.

XIV. SARCOMA AND CANCER.

'Some sicknesses besot, others enrage men, some are too swift, others too slow.'

The mortality from cancer affords a second illustration of the difficulties which arise in dealing with death-rates. A very cursory inspection of the figures shows that their interpretation is not easy. Thus considering the figures in Table XXII, figures calculated from the data given by the Registrar-General for the years 1911–1914, it is found that in the county boroughs, the urban districts, and the rural districts, the age period at which the highest cancer death-rates occur is quite significantly different. The figures in this table relate to years in which the deaths from malignant disease were carefully distributed to the districts to which they belong. The town rate is therefore not altered by the fact that many residents in rural districts go to city or urban hospitals for operation. The figures must therefore be taken as representing the truth so far as the data available at present suffice for its discovery. Considering the figures it is at once obvious that the ages at which the highest death-rates are observed to occur from cancer are very markedly differentiated between the town and the country. These differences found to exist between county boroughs and rural districts have been, after a close criticism by Professor Pearson and Dr. Tocher,

TABLE XXII. *Showing the death-rates per million at five yearly age periods from certain diseases on the data given by the Registrar-General for the years 1911–1914 among males. The figures are given separately for county boroughs, urban districts, and rural districts. The standardized death-rate is based upon the mean population 1891–1900, and the life table death-rate on Mr. King's tables.*

DEATH-RATE PER 1,000,000.

	Standardized death-rate 15+	Life table death-rate 15+	15–	25–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85+
CANCER:															
County Boroughs	1391	1985	46	120	308	737	1472	2576	4069	6100	7622	9398	9861	8971	6966
Urban Districts	1260	2014	41	107	277	584	1180	2159	3627	5382	7258	9062	9824	8802	8856
Rural Districts	1106	1993	38	97	209	499	998	1685	2938	4721	6327	8436	9846	9260	8218
VALVULAR DISEASE OF HEART:															
County Boroughs	848	1142	171	216	400	603	884	1326	1963	2958	3861	4981	5968	4967	4390
Urban Districts	698	1069	127	145	247	417	615	960	1503	2444	3693	4902	5640	5411	5382
Rural Districts	617	1096	87	116	205	327	488	767	1236	2019	3228	4994	6147	6068	6385
DIABETES:															
County Boroughs	178	239	40	61	93	94	130	230	404	611	1028	1042	1211	842	902
Urban Districts	170	249	42	61	77	83	131	198	376	703	866	1060	1037	913	651
Rural Districts	151	224	57	75	91	103	115	186	287	493	616	829	823	708	359
PNEUMONIA:															
County Boroughs	1030	1254	320	608	931	1111	1413	1615	2077	2540	2886	3253	3563	3562	4150
Urban Districts	680	888	228	370	571	680	845	1104	1292	1748	2011	2598	2518	2658	3634
Rural Districts	470	661	164	216	425	493	625	760	884	1034	1327	1794	2174	2399	3234
CIRRHOSIS OF LIVER:															
County Boroughs	189	256	2	23	113	188	379	485	628	685	784	699	535	302	120
Urban Districts	170	246	2	17	80	193	298	435	559	684	739	643	462	286	274
Rural Districts	128	198	3	22	51	142	212	283	400	558	543	484	494	348	194
BRIGHT'S DISEASE:															
County Boroughs	651	893	59	138	277	478	795	1197	1683	2467	3189	3693	3870	3282	3849
Urban Districts	538	820	49	108	202	379	574	924	1322	1985	2063	3565	3680	3380	3839
Rural Districts	403	686	44	84	146	258	360	693	907	1456	1917	2974	3150	2770	3234
PHTHISIS:															
County Boroughs	2129	2253	1259	2026	2644	2901	3163	3315	3041	2727	2118	1169	755	453	361
Urban Districts	1363	1406	925	1401	1670	1725	1787	1851	1791	1735	1182	780	456	245	171
Rural Districts	1099	1082	793	1368	1321	1312	1203	1181	1223	1049	867	713	375	252	138

considered to represent real differences quite beyond the error of random sampling. It is impossible to contradict the results of this investigation. But the problem as they treat it is stated in terms which concern statistical and not biological requirements. The effect of different environment on the physiology of the inhabitant has not been considered. The fact that the death-rate from cancer at ages 70 to 75 years is very much higher in the county boroughs than in the rural districts does not permit of any deduction until the question has been settled how far its occurrence is due to ageing of the tissues. As it has been seen that in towns the same degree of senescence is found at an earlier age than in the country, until this degree of difference has been measured, it is impossible to settle at what ages a comparison should be made between city and country death-rates.

To advance beyond this stage of the argument it is necessary to criticize the results obtained when the routine methods of calculating death-rates are applied. The standardized death-rates, taking the mean population of England between 1891–1901 as the standard population, have thus far been calculated. The values are given in Table XXII. It will be observed that judging by this measure there is considerably more cancer in towns than in country. But I do not think this measure can be considered valid. As we have already seen, a person dying in the city at the age of 50, dies on an average about six years earlier than he would have died had he lived in the country. Either this is due to premature ageing or due to greater exposure to the infective diseases of later age, namely pneumonia and bronchitis. Now cancer is commonly believed to be a degenerative disease, that is, a disease to which the ageing of the tissues predisposes. Chronic irritation rarely produces cancer in youth, but chronic irritation tends to produce cancer in middle age. In fact, the chief sites of cancer are those regions of the human body most subject to chronic irritation. The necessary allowance for the ageing of the body experienced in towns over that experienced in the country must thus first be made before any differentiation between the amounts of cancer present in different districts is justifiable, though here the possibility of local ageing of tissues must not be overlooked, a phenomenon well known when problems of local immunity are the seat of question. Thus cancer of the stomach and of the uterus are more common between the ages of 65 and 75 years than above that age, while cancer of the lip is three times more prevalent at ages over 75 years than in the previous decade.

In the case of cancer a method of comparison is, however, in our hands. Mr. King has constructed life tables for London, for the county boroughs, for the urban districts, and for the rural districts, and these tables are based on the same data as are used by Dr. Stevenson in calculating the cancer rates for each age period. A comparison between a standard and a stationary population is thus immediately possible. When the appropriate death-rates for each age group are applied to the respective age groups in a stationary population the true life table death-rates from cancer are discovered. Contrary to what we have already had reason to believe was the case, namely that cancer was more prevalent in towns, it is found that the life

table death-rate is constant. This means that, taking an equal number of persons living above the age of 15 years, exactly the same proportion is destined to die from cancer whether the individuals live in a rural district, an urban district, or in a county borough. A common criticism of such a result is that all the deaths from cancer have been grouped together and that is not medically admissible. To meet this objection the death-rates from cancer of the stomach have been taken out separately. The result is the same.

There is, however, another way of looking at the subject. It may be asked what proportion of persons attaining the age of 15 years of age in different environments are likely to die of cancer in after-life. This question can be quite easily answered from the figures given in the life tables. From the life table population as the cancer death-rates at each age are known the number of deaths above 15 years of age can at once be obtained. The life table also gives the number of persons attaining the age of 15 years. It is thus at once calculated that out of 10,000 people attaining the age of 15 years 919 are destined to die of cancer in the county boroughs, 987 in the urban districts, and 1,025 in the rural districts. Thus the paradoxical conclusion is arrived at that more cancer, an equal amount of cancer, or less cancer exists in the county boroughs than in the rural districts according as the standardized death-rate, the life table death-rate, or the survivors of those who attain the age of 15 years is taken as the criterion. This example makes plain the great care necessary in drawing conclusions from figures.

The figures given in the preceding paragraphs refer to the average of the rural districts and county boroughs of the whole country. Thus the rural districts of the south are combined with the rural districts of the north, and it is the same with the urban districts and the county boroughs. That is, when the average of the whole country is taken for rural districts, urban districts, and county boroughs, there is an exact equality in the number of persons living above the age of 15 years destined to die of cancer in these different environments. The figures for London to a certain extent represent an exception, the rates being considerably higher than those seen in the other three districts. But London is not an average of the whole of England. Therefore before theorizing it is necessary to make further inquiry. Either London has a cancer rate of its own or a large part of the underlying aetiology has not been revealed by the method by which the statistics have just been examined.

The further examination of this point would have been impossible had not the department of the Registrar-General kindly placed at my disposal a series of life table data calculated for different districts of the country but not published. We have thus information for the north of England, for Wales, for the midland, and for the southern counties of England. For the present inquiry such large districts are sufficient. In this case the rural districts in each group of counties are not separated from the included towns and county boroughs : each average is for the whole of the district. When the cancer death-rates at each age period calculated from the population and deaths in these groups are applied to the corresponding life table populations it is found that the discrepancy observed
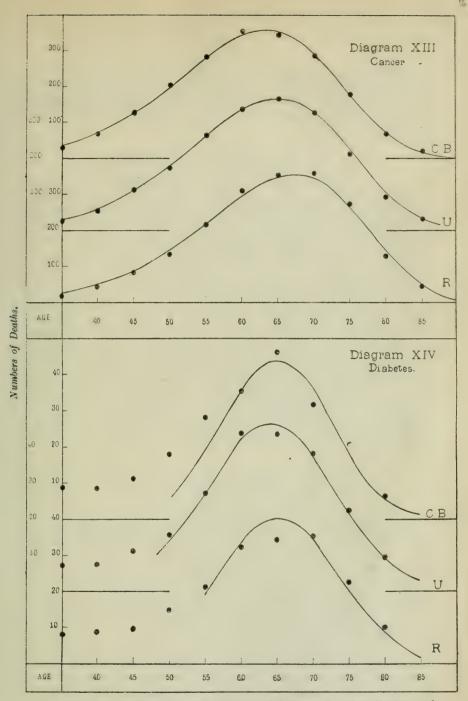
with regard to London when it was compared with the average of the rural districts and county boroughs for the whole of England is in accordance with a second general law. It is found as we pass from the north to the south that the amount of cancer very considerably increases. In the north the life table death-rate at ages above 15 is 1·78 ; in Wales and the midlands respectively 1·97 and 1·95 ; in south England 2·24 and in London 2·16. Though London thus presents a slightly lower rate than the south of England it falls in line with that district. The death-rate from cancer thus increases as the latitude decreases.

It has already been noted that an earlier age incidence of a disease such as measles in a town might be associated with more frequent epidemics of disease. Even in an adult disease such as cancer if that were due to an infection a similar phenomenon might also be present. It has been shown that the age at which the greatest number of deaths from cancer occurs in county boroughs is earlier than in the rural districts. But the argument from measles does not hold. Association with infection is not required, as in their susceptibility to the disease which is due to increasing senility persons living in towns must on the average succumb at an earlier age than persons living in the country. In consequence of this earlier senility an earlier mean age at which the disease occurs must be expected. To argue from an earlier average age at death from cancer in towns than in the country to the fact that cancer is an infectious disease is therefore impossible.

It is necessary, however, to try to estimate more correctly the difference between the age of the maximum number of deaths from cancer in the three districts. In Diagram XIII, therefore, the number of deaths occurring at each age in a stationary population is shown. It is easily observed that the age of maximum mortality in the county boroughs is at least five years earlier than the maximum age at death in the rural districts and that the form of the curves is nearly identical. The graph of urban districts mortality lies almost exactly between that of the county boroughs and that of the rural districts. The exact difference between the age of maximum fatality in city boroughs and rural districts is, however, not directly measurable. The form of the distribution of deaths, however, very closely agrees with the curve called by Professor Pearson, Type III. Such curves have accordingly been calculated and their course is shown in the diagram (Diagram XIII) by a continuous line. The difference between the maxima given by the curves for the county boroughs and the rural districts is seven and a half years. 'High aged' persons are more common in the country, 'old age' equally common.

The conclusion seems to be that the frequency of cancer is a function of senescence and can only be estimated by the method originally introduced by Dr. Farr where the appropriate stationary populations are taken as the standard population and used to calculate the respective total death-rates. It is to be distinctly understood that this function of senescence may differ in different regions, and all that has been shown is that when different

Numbers of Deaths.

CANCER.—This diagram illustrates for the rural districts, the urban districts, and the county boroughs the number of deaths due to cancer occurring at each age period above the age of 35 years in the life table populations appropriate to each group of districts. These deaths have been graduated to the curve called Type III by Professor Pearson, the actual observations being shown by black circles. The total number of deaths is in each group of districts the same. It will be observed that the age at which the largest number of deaths occur is progressively later in life the healthier the conditions of life.

DIABETES.—This diagram shows the same facts for diabetes, the graduation curve being a normal curve of error. The deaths in the life table population are again the same in the groups of districts but differ from cancer in that the age period at which diabetes is most common is constant.

C.B. = county boroughs.   U = urban districts.   R = rural districts.

environments in the same region are compared no difference in the cancer death-rates due to environment has been proved to exist.

Diagnosis has not been discussed here where method of treatment of statistics is the object in view. It is a large subject and requires special consideration.

XV. Valvular Disease of the Heart.

'She that fears to be swollen with a tympany.'

Valvular disease of the heart seems to behave in much the same way. The age of the greatest prevalence in the country is about seven years later than that in the cities. The amount, however, is much the same in all districts when judged by the life table death-rate, the two extremes only differing by 4 per cent. If, however, the standardized death-rates are used the difference is more than 30 per cent. greater in the county boroughs than in the country. This shows again the difficulty of dealing with standard populations. It is not a matter of more of the disease being present in a city, it is rather a matter of the disease developing at earlier ages. There is a greater ageing of the tissues and with this ageing the end of life is determined more quickly. The response must be an actual fact because it is certain that a person suffering from any disease of the heart in the city must be better cared for medically than a similar person living in the rural districts, for, though medicine be in many respects futile, in this case the benefits of sound treatment are undoubted. I think, therefore, that it is probable that premature ageing of the tissues is an important factor in the earlier age at death. (Diagram XV.)

XVI. Diabetes.

'If I could as easily decline diseases as I could dislike them I should be immortal.'

Diabetes like cancer is a disease in which the death-rates at different ages vary considerably in town and country when compared age by age ; but it has certain peculiarities of its own. When the death-rate is standardized in the usual fashion it is found that in the county boroughs it is in considerable excess of that in the rural districts. As with cancer when the life table populations are used it is found that the number of persons living above the age of fifteen years destined to die of diabetes is the same in town and country. But diabetes does not behave in the same way as cancer does. It has been seen that with cancer the commonest age at death in a stationary population is higher in the country than in the town by about five to seven years. In diabetes, however, whether a person lives in a rural district or in a county borough, the commonest age at death is the same. The degenerative factors which dispose to diabetes are thus of a different kind from those which predispose to cancer. This difference is in accord with what is found in other branches of the theory of immunity. It tends, however, to make the association of the two diseases in the same conditions somewhat doubtful. This association, shown to exist by Dr. Maynard with

regard to the data in the United States of America, has not been found to hold elsewhere by other observers, Greenwood finding it absent in Switzerland, and Claremont, using the variate difference method, absent in England. (Diagram XIV.)

XVII. Nephritis.
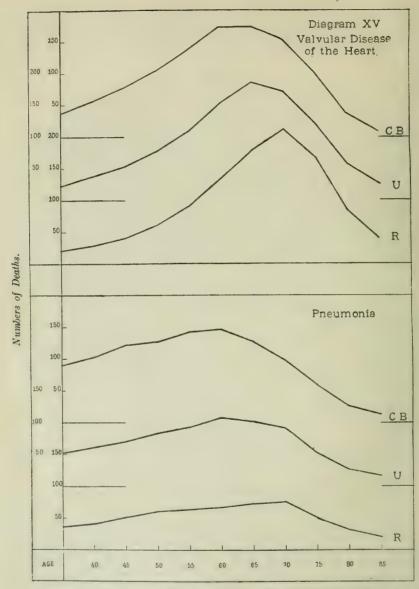
'The stone, the colic terrible as expected, intolerable when felt.'

Nephritis or Bright's Disease also shows some points of interest. In this case the disease is recognized as degenerative in a measure, though probably due to some kind of toxin produced in the alimentary tract or elsewhere. In cities the maximum number of deaths occurs between the ages of sixty and sixty-five, the same period apparently as that in which possible death from cancer is most prevalent. The change with age from town to country is such that the maximum number of deaths occur nearly 10 years later in the country than in the city. The disease, however, is much less prevalent in the country. When the life-table death-rate is taken as the appropriate measure the amount is 30 per cent. greater in the town than in the rural districts. This is in contrast to the fact that when the death-rate, calculated on a standard population, is used, the difference between the mortality in cities and in rural districts is more than 50 per cent. A problem of great interest is thus presented. It is obvious that the laws which govern the chance of death from Bright's disease with increasing age in different environments differ in much the same way as those due to cancer; however, hygiene steps in on the scene with the result that a very marked lessening in the numbers destined to succumb to the disease, termed Nephritis by the Registrar-General, is found to occur in rural as compared with city conditions. It is to be noted in this case that the relationship between the standardized and the life table death-rates cannot be expressed as a straight line. In the county boroughs the standardized death-rate gives too small a measure of incidence when the conditions obtaining in the rural districts are taken as a standard.

XVIII. Pneumonia as defined by the Registrar-General.

'He that expects to be drowned with a dropsy may be shrivelled with a fever.'

In the case of pneumonia we have a disease influenced very largely by environment. It is one of those diseases in which the standardized death-rates as found in the county boroughs, in the urban districts, and in the rural districts, are very closely correlated with the life table death-rate. In this case the relationship between the standardized death-rates and the life table death-rates is strictly linear. It is expressed by $D_2 = 1 \cdot 0589 D_1 + 163 \cdot 3$, which is accurate within $\frac{1}{3}$ per cent. The disease thus resembles phthisis in this characteristic. The manner in which the age incidence of this disease varies is shown in the diagram (Diagram XV). The difference between the ages of maximum susceptibility in town and country is about 7–10 years. The maximum occurs in the county boroughs about 60 years of age and in the country at nearly 70. At the earlier ages of life the disease is about twice as common in the town as in the country, and

64

VALVULAR DISEASE OF THE HEART AND PNEUMONIA.—This diagram shows how the number of deaths vary in a stationary population in the same groups of districts for valvular disease of the heart and pneumonia. In each of these diagrams the maximum number of deaths occur progressively later as we pass from county boroughs to urban and rural districts. The total death-rates from valvular disease of the heart is practically the same in the three groups of districts. In pneumonia, however, it is very much less in the rural districts than in the urban districts and county boroughs.

this relationship holds till the age of 60, when the numbers become nearly equal, while after 75 years of age the numbers dying in the rural districts are nearly thrice those in the towns. With such relationships of the number of the deaths it is obviously not possible to compare the death-rates at different ages in different conditions, so far as these are expressed quantitatively by means of ‘ crude ’ or ‘ standardized death-rates ’.

XIX. General Survey.

The facts given in the previous pages regarding the death-rates in different environments may now be surveyed. I think it may be taken as most probable that the most satisfactory measure of the amount of disease is a life table death-rate. The effect of two such different environments as that of a city or a rural district cannot be compared directly without considering how far the influence of the surroundings has changed the average vital processes of the individual. What happens is not known, but I think it must be admitted that a person living in city conditions tends to age more rapidly than a person living in rural surroundings. It is not merely that the infective processes, which determine deaths in old age, are more generally found in the town. It is that the conditions which tend to depress vitality also tend to produce premature senility. The range in age vitality between town and country in the years 1910–1912 is equivalent to a difference of six years. Very nearly the same figures are found to describe what happens in cancer and nephritis in the two types of districts. In both of these diseases the maximum age of death is about seven years earlier in the town than in the country, a number identical with that already found when all diseases are considered together.

If the life table death-rate be thus taken as the standard it requires to be considered how far standardized death-rates can be justified for ordinary use. It has been found that the standardized death-rate from all causes is in direct linear relation with the life table death-rates within an error not more than $\frac{1}{2}$ per cent. For general hygiene, therefore, the standardized death-rate may be considered accurate.

When special diseases are considered, however, a very different problem has to be faced. In such diseases as phthisis and pneumonia the standardized death-rates are in linear relationship with the life table death-rates. The one can be calculated directly from the other. The standardized death-rates thus fulfil their purpose. With regard to cancer, diabetes, and nephritis, it is found that the life table death-rate is constant in county boroughs, urban or rural districts. The standardized death-rate having thus no relation to the life table death-rate, cannot therefore be used as a criterion. In other words, if the correlation between the standard and life table death-rate is high, the standardized death-rate is a sound basis of deduction. If, on the other hand, it is low, no conclusion can safely be drawn.

I think, further, that comparison of death-rates from one disease at a definite age cannot be employed. The whole change in the age distribution of disease is part of a general process, and to compare, for instance, the death-rate from cancer in town and country, between

the ages of 55 and 65 years is to compare sections of the population which consist of different elements, as it has been rendered probable that the inhabitant of the country is at these ages biologically about six to seven years younger than the inhabitant of the town.

PART II. MATHEMATICAL TREATMENT
XX. Introduction.

Having discussed the main points with reference to death-rates and the connexion between hygienic conditions and the death-rate, it remains briefly to give a description of the different methods by which those desirous of making inquiry into health conditions may most conveniently work. For many purposes it is necessary to calculate one or other of the life table data, and the more easily this can be done the more likely is investigation to be undertaken. It is proposed in this section to give first a general theory of life table mathematics and to follow this by examples of the method of calculation. The mathematical theory is given in a form which I think is new, but the equations are so simple that it is highly probable that they have been published already. Methods of calculating devised by Dr. Snow and myself follow. Some of the methods given by Dr. Snow are essentially the same as those used by myself, though arrived at independently, but there are differences. Dr. Snow's method is to calculate, first the number of survivors at any age ; from thence derive the population and the expectations. I prefer to calculate the expectations and the number of survivors separately, and obtain the population by multiplication. For an individual life table, probably my method will take longer than Dr. Snow's, but if a large number are required, and if half a dozen or more are calculated at the same time, the fact that constant multipliers are used will probably render my method the more convenient. The relative convenience of both must, however, be tested in practice. It is to be noted that my method has been devised to use the data in the form in which they are recorded by the Registrar-General. The populations, deaths and death-rates are given by him for the registration districts in separate years of life up to 5 years : in five yearly age groups of life up to 25 years : in ten yearly age groups from this to the age of 75 years, while above this age no further age distinction is made. The mathematical section which follows need not be read except by those interested in the subject as the description of the technique is practically quite independent of the theory.

XXI. Mathematical Theory.

The general theory of the life table when the expectation of life is taken as the fundamental function is much more easy than when the death-rate is chosen. The former leads to very simple formulae, the latter to a mathematic which is itself cumbrous and also unsuitable for the purpose of calculation. In what follows the common notation with one exception is used. It is a matter of regret that actuaries have chosen the letter e to denote the expectation. It is already reserved by long convention to denote the base of the natural logarithms, and as these occur largely in the theory, some other symbol for the expectation must be chosen.

I
Notation.

$x =$ age.

$l_x =$ number of survivors at age x.

$\mu_x =$ instantaneous death-rate

$$= -\frac{1}{l_x}\frac{dl_x}{dx}.$$

$E_x =$ expectation of life at age x

$$= \frac{\int_x l_x dx}{l_x}.$$

$D_x =$ life table death-rate, i.e. the death-rate of all persons living in a stationary population above the age x.

$$= \frac{1}{E_x}.$$

$T_x =$ the total population living above the age x.

$L_{x \cdot y} =$ the population living between the ages x and y.

$$= T_x - T_y.$$

II

The mathematical relationships of the quantities just defined, when the expectation of life is taken as the fundamental function, can be shown in a few lines.

Since
$$E_x = \frac{\int_x l_x dx}{l_x} \tag{1}$$

$$\frac{dl_x E_x}{dx} = -l_x$$

and
$$E_x \frac{dl_x}{dx} + l_x \frac{dE_x}{dx} = -l_x$$

whence
$$\mu_x = -\frac{1}{l_x}\frac{dl_x}{dx} = \frac{1}{E_x} + \frac{1}{E_x}\frac{dE_x}{dx}. \tag{2}$$

Integrating
$$l_x = \frac{1}{E_x}e^{k-\int\frac{dx}{E_x}} \quad \text{where } k \text{ is a constant.} \tag{3}$$

Integrating a second time we have

$$T_x = e^{k-\int\frac{dx}{E_x}}. \tag{4}$$

If the life table death-rate D_x or the reciprocal of the expectation be substituted, these formulae become respectively :

$$\mu_x = D_x - \frac{1}{D_x}\frac{D_x}{dx}. \tag{2^1}$$

$$l_x = D_x e^{k-\int D_x dx} \tag{3^1}$$

$$T_x = e^{k-\int D_x dx} \tag{4^1}$$

E 2

XXII. On the Calculation of Life Table Death-rates and Expectations.

The method of calculating the life table death-rates and the expectations has been described in the Sections VII and VIII, but to make this technical part complete, an example of the use of the method is given. As will be remembered, it essentially depended on the fact that if the death-rate of a standard population is known for all individuals above a definite age a suitable series of relationships can be found, which will give the life table death-rate and immediately the expectation by taking the reciprocal. The standard population chosen for which the equations of relationship are given is that which is in arithmetical progression. The example chosen for illustration (Table XXIII) is the registration district of Liverpool for the decade 1891–1900 : the males alone are employed. The standard population of those living at each age is given in the first column ; the death-rates in the Liverpool registration district in the second column ; the number of deaths obtained by multiplying the death-rates into the standard population in the third column ; the sum of these totals from each age and upwards in the fourth. Thus the figure opposite 55 is the sum of the deaths occurring above the age of 55 years, in the three age groups 55–65 years, 65–75 years, and 75 years and upwards. It is only necessary to put the figures in the fourth column in the appropriate equation given previously in Table XVI (p. 37), to obtain the life table death-rates. These are given in the fifth column, and in the sixth column the expectations or the reciprocals. It is not necessary, in view of the length of discussion previously given, to say any more upon this subject.

TABLE XXIII. *Showing the method of calculating life table death-rates and expectations.*

Age group.	Population.	Death-rate Liverpool, 1891–1900.	Deaths.	Age.	Sum of Deaths above each age.	L. T. death-rate.	Expectation.
0–5	16	121·19	1939·04	0	5205·03	35·029	28·55
5–10	15	19·42	141·30	5	3265·99	24·617	40·62
10–15	14	4·64	64·96	10	3124·69	27·116	36·83
15–20	13	7·43	96·59	15	3059·73	29·843	33·51
20–25	12	9·78	117·36	20	2963·14	33·464	29·88
25–35	21	16·63	349·23	25	2845·78	37·908	26·38
35–45	17	28·89	491·13	35	2496·55	49·308	20·28
45–55	13	44·95	584·35	45	2005·42	65·194	15·34
55–65	9	71·00	639·00	55	1421·07	89·938	11·12
65–75	5	116·52	582·60	65	782·07	131·461	7·61
75–85	1	199·47	199·47	75	199·47	203·018	4·93

XXIII. On Graduation of the Life Table Death-rates and Expectations.

For the purpose of observing the relationship between different life tables, the life table death-rates were graduated in Section X to the formula $a(c-x)^{-n}$, or in the form used for calculation

$$\log D = \log a - n \log (c - x) \qquad (5)$$

or $$\log E = -\log a + n \log (c - x) \qquad (5')$$

The method by which this is done is to choose the three values of the expectations at equal age distances and then solve for the constants. For example the expectations in the Manchester life table at 15 years, 45 years, and 75 years of age are respectively, 38·78 years, 17·80 years, and 5·11 years. Taking the logarithms of the expectations we obtain the following three equations :

$$1\cdot58861 = -\log a + n \log (c-15) \qquad (6)$$
$$1\cdot25042 = -\log a + n \log (c-45) \qquad (7)$$
$$0\cdot70842 = -\log a + n \log (c-75) \qquad (8)$$

Subtracting (7) from (6) and (8) from (7), we have

$$0\cdot33819 = n \log (c-15) - n\log (c-45) \qquad (9)$$
$$0\cdot54200 = n \log (c-45) - n\log (c-75) \qquad (10)$$

Dividing (9) by (10)

$$0\cdot62397 = \frac{\log (c-15) - \log (c-45)}{\log (c-45) - \log (c-75)} \qquad (11)$$

This equation is difficult to solve : the value of c can be found to be 112·164. It is hoped soon to publish a table by which this and similar equations can be solved by reference to a series of calculated values. From the value we obtain immediately

$$n = 2\cdot1088$$
$$\log a = 2\cdot60265$$
$$a = 400\cdot54$$

A second method of graduating the expectation is to consider the life table death-rate given by the formula :

$$D_x = al^x + bm^x \qquad (12)$$

This formula graduates many life tables with extreme accuracy, and the solution is quite easy. Taking four values A, B, C, and D of the life table death-rates at equal intervals of age, say p years, and forming the equations, we have

$$\begin{aligned} A &= a + b \\ B &= al^p + bm^p \\ C &= al^{2p} + bm^{2p} \\ D &= al^{3p} + bm^{3p} \end{aligned} \qquad (13)$$

The solution of these equations is found at once to be given by :

$$l^p m^p = \frac{BD - C^2}{AC - B^2} = K. \qquad (14)$$

$$l^p + m^p = \frac{AD - BC}{AC - B^2} = L. \qquad (15)$$

so that
$$l^p - m^p = \sqrt{L^2 - 4K}. \qquad (16)$$

whence l^p and m^p are at once determined, and thence a and b from the original equations :

$$a = \frac{B - Am^p}{l^p - m^p} \qquad b = A - a. \qquad (17$$

An example of the working is shown in the next section.

XXIV. Construction of a Life Table from the Graduated Expectations or Life Table Death-rates.

In this section a short note will be given on the method of calculating the different life table constants by means of these graduations. The first method is that in which the life table death-rate is graduated to $a(c-x)^{-n}$. This method of graduation has a great defect in that it holds only between 10 and 75 years, and consequently from the information at our disposal beyond these years no extrapolation is possible. The formula, however, for T_x is as follows :

$$T_x = e^{k - \frac{a}{(n-1)(c-x)^{n-1}}} .$$
(18)

The second method of graduation affords more extensive information. To illustrate this the whole process of calculating a life table has been worked out and compared with Mr. King's Table E_8. In the first instance the life table death-rates have been calculated by the method given in Section XXII. These death-rates are shown in the first column of Table XXIV. The next step is to take the life table death-rates at 15, 35, 55, and 75 years as basis of the calculations.

Using equation (13) we have

$$
\begin{aligned}
0 \cdot 02061 &= a \quad + b \\
0 \cdot 03159 &= a l^{20} + b m^{20} \\
0 \cdot 05930 &= a l^{40} + b m^{40} \\
0 \cdot 15324 &= a l^{60} + b m^{60}
\end{aligned}
$$
(19)

whence

$$
\begin{aligned}
l^{20} m^{20} &= 5 \cdot 905870 \\
l^{20} + m^{20} &= 5 \cdot 730294
\end{aligned}
$$
(20)

whence

$$
\begin{aligned}
l^{20} &= 4 \cdot 382776 \\
m^{20} &= 1 \cdot 347518
\end{aligned}
$$
(21)

From these

$$
\begin{aligned}
a &= 0 \cdot 00125777 \\
b &= 0 \cdot 01935223
\end{aligned}
$$
(22)

As the quantities to be calculated proceed by intervals of ten and five years the second and fourth roots of l^{20} and m^{20} are required :

$$
\begin{array}{ll}
l^{10} = 2 \cdot 093508 & m^{10} = 1 \cdot 160826 \\
l^{5} = 1 \cdot 446895 & m^{5} = 1 \cdot 077416
\end{array}
$$
(23)

Multiplying a and b consecutively by l^5 and m^5 and adding, we get the life table death-rates at 20 and 25 years ; following this by multiplying by l^{10} and m^{10} the values at 35, 45 years, &c. It is well to do this throughout, and thus the values calculated can then be checked by the original equations at ages 35, 55, and 75 years. The graduated values are given in the second column of Table XXIV.

In the subsequent discussion, Naperian logarithms are used. This saves a good deal of trouble, and as a table quite efficient for the purpose exists in *Dale's Five Figure Mathematical Tables* (London : Edwin Arnold, price 3s. 6d.), no difficulty lies in the way of their use.

To obtain T_x we have

$$T_x = e^{k - \int p_x dx}$$
$$= e^{k - a \frac{l^x}{\log l} - b \frac{m^x}{\log m}}. \qquad (24)$$

Log l and log m are immediately obtained from the table of Naperian logarithms. It is to be noted that the values already found are l^5 and m^5, and not l and m, so that if the logarithms of these quantities are looked up they must be divided by 5.

Taking logarithms, we have

$$\log T_x = k - \frac{a l^x}{\log l} - \frac{b m^x}{\log m} \qquad (25)$$

where it is to be noticed that $a l^x$ and $b m^x$ have already been calculated in graduating the life table death-rate, and have only to be multiplied by reciprocals of log l and log m.

The next stage in the calculation is carried out by assuming a value of T_x. In this case as we are comparing the values obtained by this method and by the ordinary actuarial method, with regard to the data on which E_8 was constructed, Mr. King's value of T_x at the age of 15 years is selected as the starting-point. To obtain the constant k, the value of the second part of the expression at the age of 15 years must be added to log T_x, and the subsequent values of the function subtracted at each successive age.

$L_{x \cdot x+5}$, $L_{x \cdot x+10}$ are obtained by subtracting the value T_{x+5} or T_{x+10} from T_x: l_x by multiplying a value of T_x by the corresponding life table death-rate. The whole results are given in the table. The correspondence of fact and theory is very close. For nearly all the purposes for which a life table is required in hygiene they are more than sufficiently accurate. The extrapolation is found to be of very considerable accuracy. In fact the expectation at 95 years, namely 1·90 years, is, I think, more accurate than Mr. King's value of 2·43 years. The data at these high ages tend to have an error which renders Mr. King's values subject to suspicion. The tendency at such high ages seems to be for living persons to record a higher age in the census paper than their friends give to the registrar on the act of death. As Mr. King's project was to graduate the data as he found them, this consideration was not introduced. It is not necessary to present further comparisons. The figures relating to many tables have been examined and the fitting found good. The rural districts and county boroughs life tables, for instance, have been graduated in exactly the same way, and show very nearly as close a correspondence.

A third method, however, can be used to calculate the T_x and l_x columns from the expectations or life table death-rates by the use of the formula :

$$cx = \log a - nE - \log E \qquad (26)$$

where log E is the natural logarithm. This formula I have fully discussed elsewhere, and it is not necessary to repeat the argument

TABLE XXIV. *Construction of a life table by means of the graduation* $D_x = ab^x + lm^x$.

Age Period.	Life Table Death-rates.		Expectations.			T_x.		l_x.		L_{x+5} or L_{x-x+1w}.	
	Calculated.	Graduated.	Calculated.	Graduated.	Mr. King's.	Calculated.	Mr. King's.	Calculated.	Mr. King's.	Calculated.	Mr. King's.
15	0·020610	0·020610	48·52	48·52	48·57	390,781	390,781	8,054	8,047	40,029	39,970
20	0·022655	0·022670	—	44·11	44·21	350,752	350,811	7,952	7,935	39,429	39,311
25	0·025047	0·025497	—	39·85	40·00	311,323	311,500	7,813	7,787	76,139	76,163
35	0·031590	0·031590	31·66	31·66	31·71	235,004	235,337	7,424	7,422	71,514	71,560
45	0·041886	0·041812	—	23·92	23·92	163,490	163,777	6,836	6,846	64,052	64,132
55	0·059300	0·059300	16·86	16·86	16·89	99,438	99,045	5,897	5,901	51,831	51,822
65	0·091146	0·091371	—	10·94	10·99	47,607	47,823	4,350	4,352	33,083	33,270
75	0·153240	0·153240	6·52	6·52	6·49	14,524	14,553	2,226	2,243	12,708	12,711
85	—	0·276645	—	3·61	3·72	1,816	1,842	503	496	1,774	1,785
95	—	0·527890	—	1·90	2·43	42	57	22	24	42	57

by means of which it was deduced. Its convenience must be its
only recommendation. Differentiating (26) we have :

$$cdx = -ndE - \frac{dE}{E} \qquad (27)$$

so that the formula (4) for a number of persons living above any
age becomes

$$T_x = e^{k + \int \left(\frac{n}{c} \frac{dE}{E} + \frac{1}{c} \frac{dE}{E^2} \right)}$$

$$= e^{k + \frac{n}{c} \log E - \frac{1}{cE}} . \qquad (28)$$

As an example of the method the expectations in E_8 have been
chosen at the ages 15, 45, and 75, as calculated by the method in
Section XXII.

This gives the equations :

$$
\begin{array}{ll}
15c = \log a - n \ 48\cdot520 - 3\cdot88198 & (1) \\
45c = \log a - n \ 23\cdot872 - 3\cdot17271 & (2) \qquad (29) \\
75c = \log a - n \ \ 6\cdot523 - 1\cdot87533 & (3)
\end{array}
$$

Subtracting (1) from (2) and (2) from (3)

$$
\begin{array}{ll}
30c = 24\cdot648 \ n + 0\cdot70927 & (5) \\
30c = 17\cdot349 \ n + 1\cdot29738 & (6)
\end{array}
$$

Subtracting (5) from (6)

$$0 = 7\cdot299 \ n - 0\cdot58811$$

Whence $\qquad n = 0\cdot080574$

and $\qquad c = 0\cdot089842$

whence $\qquad \frac{n}{c} = 0\cdot89685$

$$\frac{1}{c} = 11\cdot1307$$

Taking logarithms in equation (28)

$$\log T_x = k + \frac{n}{c} \log E - \frac{1}{cE}$$

$$= k + 0\cdot89685 \log E - 11\cdot1307 \ D.$$

The value of k is chosen to give the initial value desired.   In this
case, putting the expectation at 15 years into the equation and taking
$\log T_x = \log 39078$, the value of T_x in Mr. King's table, we get

$$k = 7\cdot32112.$$

The values of T_x obtained from the graduation, multiplied by the
corresponding life table death-rates, give the value of l_x. The com-
parisons are given in Table XXV.

TABLE XXV.

| | T_x. | Graduated | | | l_x. | Graduated | |
Age.	Mr. King's.	in one stage.	in two stages.	Mr. King's.	in one stage.	in two stages.
15	39,078	39,078	39,078	80,465	80,540	80,540
20	35,081	35,089	35,047	79,344	79,494	79,381
25	31,150	31,224	31,143	77,870	77,959	78,013
35	23,534	23,580	23,515	74,219	74,489	74,284
45	16,378	16,323	16,385	68,459	68,377	68,637
55	9,965	9,846	9,930	59,012	58,387	58,885
65	4,782	4,698	4,732	43,523	42,820	43,127
75	1,455	1,477	1,462	22,425	22,634	22,404

The error is in most places less than 1 per cent. The greatest at 65 years is about 2 per cent. It is to be observed, however, that a very severe test of the graduation has been made by fitting to these values of the expectations separated by 30 years each. When the process is continued in two stages an almost perfect fit is obtained. The stages chosen in this case were 15–35 years and 35–75 years. Extrapolation here cannot be easily used, as the expectation can only with difficulty be calculated from the age in formula (26).

XXV. The Calculation of Life Tables by other Short Methods.

For general hygienic purposes there are two parts of a life table which are of the greatest importance. One is that which concerns the age periods from birth to 10 years, and the other for ages over 10 years. This age marks a dividing period at which the diseases of childhood have largely disappeared to give way to the causes of death which affect young adults and the later ages of life. The age period over 10 years is of great importance. These are the ages at which the problems of industrial hygiene arise. Some easy method of examining the effects of industry on health are thus necessary. The method proposed here is essentially the same as that given by Dr. Snow. It was, however, arrived at independently, and the method of construction has a slightly different principle.

The method proposed is as follows. It is assumed that if r be the mean death-rate between two ages, separated by a number of years n, l_{x+n} can be obtained from l_x by multiplying by a factor of the form

$$1 - nr + bn^2r^2,$$

where b is a constant to be determined by the comparison of the data in life tables constructed by the usual method. The calculations are based on five life tables : C, E_6, E_8, H_2, and R. The constant b has been calculated by means of least squares, and its value is given in the accompanying table for both males and females. All that is necessary is to choose an appropriate value of l_x and apply the formula.

Table XXVI. *Showing the values of b for use at different ages in the coefficient* $1 - nr + bn^2r^2$.

Age period.	Males. b.	Females. b.
10	0·0	0·0
15	0·0	0·0
20	0·0	0·0
25	0·4012	0·3611
35	0·3768	0·3894
45	0·3853	0·3763
55	0·3951	0·3868
65	0·3599	0·3660

The method of writing is shown in Table XXVII,

TABLE XXVII.

Age period.	nr.	n^2r^2.	bn^2r^2.
25–35	0·0551	0·00304	0·00122
35–45	0·0960	0·0922	0·00347
45–55	0·1784	0·03182	.0·01226
55–65	0·3560	0·1267	0·05006
65–75	0·7424	0·5512	0·19848

taking the county borough life table C. The first column contains the death-rates multiplied by ten as the interval in the calculations is ten years ; the second the square of this or a hundred times the square of the death-rate ; the third column the values of the squares multiplied by the appropriate values of b. The procedure for this is as follows. Starting with 95757, the value of l_x at 25 years of age in life table C, this number is multiplied by the corresponding number in the first column, the product subtracted from 95757 and to the resulting number the product of 95757 and the corresponding number in the third column is added. Thus l_{35} is obtained from l_{25} by subtracting $l_{25} \times 0·0551$ and adding $l_{25} \times 0·00122$, or the change may be made in one operation. The same process is repeated. With a calculating machine the process is rapid and continuous. T_x is obtained by multiplying l_x by the life table death-rate and $L_{x \cdot x + 10}$ by subtraction. The result of the process is given and compared with Mr. King's in Table XXVIII. In the second and third columns the l_x is compared ; in the fourth and fifth T_x, and in

TABLE XXVIII.

Age period.	L.T.D.R. based on arithmetical progression.	l_x.		T_x.		$L_{x \cdot x + 10}$.	
		Mr. King's.	Calcu- lated.	Mr. King's.	Calcu- lated.	Mr. King's.	Calcu- lated.
25	0·026610	95,759	95,759	361,949	359,862	93,372	92,957
35	0·033944	90,598	90,599	268,577	266,905	86,717	85,783
45	0·045393	82,183	82,216	181,860	181,122	75,859	75,133
55	0·064682	68,492	68,557	106,001	105,989	58,581	58,358
65	0·099899	47,452	47,583	47,420	47,631	34,633	34,560
75	0·166030	21,346	21,701	12,787	13,071	12,787	13,071

the sixth and seventh columns the corresponding values of $L_{x \cdot x + 10}$ or the populations living during each ten-yearly period are shown. A test of the use of this method is given with regard to cancer. If the death-rates from cancer as found to exist in the county boroughs of England between the years 1911 and 1914 are multiplied into the corresponding populations, both as given by Mr. King and as calculated here, the values of the death-rates from cancer per 1,000 of persons living above 25 years are respectively 2·75 and 2·73. As no statistical conclusion could be drawn from such a difference, it is obvious that the method is sufficiently accurate. The example given, that of the county boroughs, is of those tested, the one in which the methods give the greatest divergence. The method is even sufficiently accurate if applied to Manchester Township (M.) 1881–90.

XXVI. Dr. Snow's Method of Calculating Life Tables.

Dr. Snow's method of forming a life table proceeds very much on the same assumptions as those given in the preceding paragraph. Basing his calculations on the data of the life table for England and Wales for the years 1910–12, he forms a series of multipliers by which l_{x+5} or l_{x+10} can be obtained from l_x. These multipliers denoted by p are in general quadratic functions of the mean death-rate at each age group, denoted by r. The expression for calculating p are, however, complex, and had calculations to be made in each individual case there would still be a good deal of work to do. To obviate this a series of tables have been constructed, from which, given the value of r, the appropriate value of p can at once be read off. So far there is agreement between Dr. Snow's method and my own. The next step is different : Dr. Snow has invented a new function which he denotes by the letter k. Knowing the value of p, the appropriate value of k is obtained again from a table of the function. When k is multiplied into the corresponding value of l_x the product is $\frac{1}{2} l_x + L_{x \cdot x+5} - \frac{1}{2} l_{x+5}$ or $\frac{1}{2} l_x + L_{x \cdot x+10} - \frac{1}{2} l_{x+10}$ according as the group is quinquennial or decennial. From this Dr. Snow obtains the expectation by summing, dividing by l_x and subtracting 0·5. The working is shown in the accompanying table which illustrates the construction of a life table for the county boroughs of England and Wales. The correspondence of the expectations obtained by this method and those in Mr. King's extended table is very close, the error never amounting to more than a month.

Table XXIX.

Age group. (1)	Death-rate (r). (2)	Chance of surviving throughout Period ($n'x$). (3)		l_x. (4)	k_x. (5)	$l_x \times k_x = L'_x$. (6)	$S(L'_x) = T'_x$ (7)	$E_x = \dfrac{T'_x}{l_x} - \frac{1}{2}$ (8)	E_x in extended Table. (9)
10–15	0·00215	0·9894	(10)	10,000·0	4·9796	49,796	512,866	50·78	—
15–20	0·00321	0·9835	(15)	9,894·0	4·9683	49,156	463,070	46·30	46·28
20–25	0·00407	0·9798	(20)	9,730·7	4·9613	48,277	413,914	42·04	41·99
25–35	0·00511	0·9463	(25)	9,534·1	9·7770	93,215	365,637	37·85	37·80
35–45	0·00960	0·9074	(35)	9,022·1	9·6204	86,796	272,422	29·69	29·65
45–55	0·01784	0·8337	(45)	8,186·7	9·3225	76,321	185,626	22·17	22·13
55–65	0·03560	0·6922	(55)	6,825·3	8·7118	59,461	109,305	15·51	15·48
65–75	0·07424	0·4559	(65)	4,724·5	7·602	35,916	49,844	10·05	9·99
75–85	0·1508	0·1808	(75)	2,153·9	5·746	12,376	13,928	5·97	5·99
85 and upwards	0·2764	0·0417	85	389·4	3·860	1,503	1,552	3·49	3·55
	—	—	95	16·2	3·00	49	—	—	—

The ease of applying Dr. Snow's method depends on the series of tables which have been constructed and which are published by the Registrar-General. Any one, therefore, desiring to use it must procure these tables. In many ways they represent a great advance. One disadvantage is that it does not give the T_x in the form suitable for calculating life table death-rates for different diseases, another operation being required, namely, the subtraction of half of l_x. The method of working is as follows. (Table XXIX.)

The death-rates (r) in the different age groups are tabulated in column (2). The values of p corresponding to these values of r are then taken from the tables and entered in column (3). Beginning at the age of 10 years and taking l_{10} equal to 10,000, successive multiplications by the values of p in column (3) are carried out and entered in column (4). For example, l_{20} is obtained by multiplying l_{15} by 0·9835 and so on. The values in brackets are the values of x in l_x. The values of k corresponding to the values of p in column (3) are now taken from the tables and entered in column (5). Column (6) contains the products of the numbers in columns (4) and (5), and column (7) the successive sums for each age and upwards. Column (8) is obtained by dividing the numbers in column (7) by those in column (4) and subtracting 0·5. These numbers are the complete expectations of life at the ages shown in brackets in column (4). Column (9) gives for comparison the expectations in Mr. King's extended table.

XXVII. Analysis of Phthisis Death-rate.

In Section XIII, referring to phthisis, a note was made upon the analysis of the disease into several components, each of which might be found to exist almost alone in different environments or industries. The method of analysis is given here with the figures adjusted so as to permit the standard death-rate from each type of phthisis to be calculated directly. It is to be noted that though applied to phthisis the method is also applicable to other health problems. There are some classes of disease which are mixed up in the returns given by the Registrar-General, and which cannot well be separated. Thus many cases of osteo-arthritis may be grouped with rheumatoid arthritis. There is no reason, however, why, if two diseases have different age distributions, and if they occur in varying amounts in different places, their statistical separation on the lines developed should not be possible. The problem of deaths from heart disease suggests particular analysis. Such questions, however, are complex, and no one need enter on such an investigation unless he is willing to face a good deal of arithmetic.

In Table XXX the coefficients a, b, and c denote respectively the age period death-rates from 'young adult', 'middle age', and 'old age' phthisis, adjusted so as to give, on solution of the equation, the standardized death-rate for each type of the disease. The values on the right-hand side of the equation are the phthisis death-rates. The working of the left-hand side of the equation is identical in every instance, while the numbers to be analysed are given by the figures on the right. To reduce the nine equations to three, namely those denoted by (1), (2), and (3), the procedure is as follows. To obtain the number in equation (1), the figure on the right-hand side of each of the nine equations is multiplied by the corresponding coefficient of a. Thus 31 is multiplied by 31, 100 multiplied by 100, and 178 by 192, and so on. The numbers are then added. With any calculating machine the process is continuous. To obtain the figures in equation (2) the same numbers

on the right hand in the nine equations are multiplied by the co-efficients of b, and summed. Equation (3) is obtained likewise by multiplying by the coefficients of c. Having obtained these numbers, the subsequent arithmetic is plain sailing.

TABLE XXX.

Analysis of Death-rates among Males.

Age Group.	Young Adult.		Middle Age.		Old Age.		Phthisis Death-rate, Essex.
10–15	31a	+	8b	+	22c	=	31
15–20	100a	+	35b	+	31c	=	100
20–25	192a	+	74b	+	39c	=	178
25–35	176a	+	129b	+	61c	=	236
35–45	97a	+	175b	+	109c	=	287
45–55	51a	+	173b	+	191c	=	290
55–65	27a	+	126b	+	305c	=	264
65–75	14a	+	64b	+	307c	=	193
75+	8a	+	26b	+	128c	=	81

The solution in one case, namely, that for Essex, is given. The method of forming equations (1), (2), (3), is described in the text.

$$91{,}800a + 70{,}964b + 55{,}877c = 139{,}780 \quad (1)$$
$$70{,}964a + 104{,}608b + 125{,}540c = 195{,}481 \quad (2)$$
$$55{,}877a + 125{,}540b + 258{,}707c = 261{,}932 \quad (3)$$

Dividing each equation by the coefficients of a.

$$a + 0{\cdot}773028b + 0{\cdot}608682c = 1{\cdot}522658 \quad (\text{I})$$
$$a + 1{\cdot}474100b + 1{\cdot}769066c = 2{\cdot}754650 \quad (\text{II})$$
$$a + 2{\cdot}246720b + 4{\cdot}629937c = 4{\cdot}687653 \quad (\text{III})$$

Subtracting (I) from (II), and (II) from (III)

$$0{\cdot}701072b + 1{\cdot}160384c = 1{\cdot}231992$$
$$0{\cdot}772620b + 2{\cdot}860871c = 1{\cdot}933003$$

Dividing each equation by the coefficients of b.

$$b + 1{\cdot}655157c = 1{\cdot}757297 \quad (\text{IV})$$
$$b + 3{\cdot}702818c = 2{\cdot}501881 \quad (\text{V})$$

Subtracting
$$2{\cdot}047661c = 0{\cdot}744584$$
$$\therefore c = 0{\cdot}363627$$

To obtain b, put the value of c in equation (IV),
giving b = 1·155435

To obtain a, put the values of b and c in equation (I),
giving a = 0·408141

The standard death-rates due to each type of phthisis are thus found to be :

Young adult = a = 0·408141
Middle age = b = 1·155435
Old age = c = 0·363627

Analysis of Death-rates among Females.

Age Group.	Young Adult.		Middle Age.		Old Age.	
15–20	126a	+	57b			=
20–25	145a	+	76b			=
25–35	140a	+	123b			=
35–45	90a	+	154b	+	22c	=
45–55	60a	+	121b	+	67c	=
55–65	37a	+	75b	+	400c	=
65–75	11a	+	25b	+	867c	=
75+	3a	+	19b	+	200c	=
	69,700a	+	59,649b	+	30,937c	=
	59,649a	+	69,122b	+	66,970c	=
	˙0,937a	+	66,970b	+	956,662c	=

Dividing each equation by the coefficients of a.

$$a \;+\; 0.855796b \;+\; 0.443859c \;=$$
$$a \;+\; 1.158812b \;+\; 1.122735c \;=$$
$$a \;+\; 2.164722b \;+\; 30.922908c \;=$$

Subtracting (I) from (II), and (II) from (III)

$$+\; 0.303016b \;+\; 0.678876c \;=$$
$$+\; 1.005910b \;+\; 29.800173c \;=$$

Dividing each equation by the coefficients of b.

$$b \;+\; 2.240397c \;=$$
$$b \;+\; 29.625089c \;=$$

Subtracting

$$+\; 27.384692c \;=$$
$$\therefore c \;=$$

To obtain b, put the value of c in equation (IV),

$$\text{giving } b \;=$$

To obtain a, put the values of b and c in equation (I),

$$\text{giving } a \;=$$

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MEDICAL RESEARCH COUNCIL

No. 61

EXPERIMENTAL RICKETS

BY

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Medical Research Council.

EXPERIMENTAL RICKETS

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CONTENTS

[1] The spelling 'vitamin' has come into general use since this Report was set in type.

I. INTRODUCTION

THE experimental work and results to be described in this paper are the outcome of an investigation into the cause of rickets extending over the last five years. The work is being actively prosecuted and the publication is to be regarded as of an interim nature. Two earlier accounts (1) have already been published both representing lectures given at institutions. In neither case was it possible to present more than a small amount of evidence in support of the deductions made, and it seemed desirable that a publication which supplies more evidence and fuller experimental details of the work performed should be forthcoming. It is not thought that any part of the research is complete but it has reached a stage when several points of practical importance as regards rickets are established and evidence of these facts is now offered.

As the work has proceeded, it has necessitated the introduction of more accurate and refined methods, which have made many of the earlier experiments appear crude. Points which were considered as of little account now appear of greater importance and vice versa. In spite, however, of the crudeness of the earlier work, I shall describe some of it; for it is the refining process that results from prolonged research of this type which illustrates more vividly the relative importance of the facts and adds to the interest by revealing the difficulties encountered.

The investigation was undertaken in the first place to find the actual cause or causes of rickets and the work was made as comprehensive as possible. When I was satisfied that some of the most important of these were established, it was then necessary to examine each factor more closely and especially in relation to the other causative agents. The closer examination carried out under precise conditions obviously resulted in a more balanced view as to the relative importance of the facts, as well as leading to more correct interpretations of the experimental results.

All dietetic problems must ultimately submit to quantitative experiment. During the earlier experimental period only qualitative work was possible. Any one with experience of feeding experiments must be aware of the difficulty of getting most animals to eat measured amounts of food when the diets are not physiologically complete. The fact that such diets tend to produce ill health militates against complete success along these lines, and it is only after much experience that it is possible to obtain dietetic mixtures which, while producing results quickly, are eaten completely and with relish.

A criticism that can be made against work of this nature is that, to ensure success, it is essential that the experiments should be made on animals of the same type and breed and that, when absolute comparison is wanted, only puppies of the same litter should be used. To those who think that heredity plays an important part in

the aetiology of rickets, this criticism will particularly appeal. My attitude, as I imagine is that of most physiologists, is to place the hereditary factor as the cause of a particular disease in the last category for investigation and to bring it into prominence only when all other explanations fail. It is quite possible that heredity may be of some importance in rickets, but it has not up to the present materially interfered with the results of these experiments so far as I have been able to observe.

It is true that I have attempted to work on litters of puppies so far as was possible but results will be given and deductions made, more particularly in the earlier experiments, when no such condition holds. Work of this nature is much simpler when each animal is comparable with another animal but, on the other hand, experiments on dissimilar animals certainly lead to results which might be missed working under the more ideal conditions. Such factors, for instance, as size and weight, rate of growth and general habits of the various types of puppy, all of which, as will be seen, are of great importance in the study of rickets, stand out prominently before the investigator when, as has happened in some of the earlier experiments, any puppy which could be procured was investigated. There is also as great a difference in the weight, rate of growth, and general habits of individual children as there is in puppies, and the disease in children is the ultimate problem awaiting solution.

The work to be described has been done on a very large scale involving the dieting of nearly 400 puppies, and it will be seen to include the whole problem of nutrition. A moment's consideration would lead one acquainted with the science of dietetics to foretell the unlimited nature of a problem of this type. It is true that recent investigations of deficiency diseases such as beri-beri and scurvy have been circumscribed and yet apparently so satisfactory that it would appear that a nutritional disease may be very limited in its aetiology ; but this does not hold in rickets. In fact there is a temptation to suggest that knowledge of both beri-beri and scurvy would be greatly increased if the experimental methods were extended to include the consideration of other elements of diet and mode of life, as well as the respective vitamines involved in the diseases. This has been done to some extent by Braddon and Cooper (5) and Funk (6), and, as the result, there is evidence that carbohydrate plays a part in the development of avian polyneuritis. It may happen that, in the case of beri-beri and scurvy, as in this rickets investigation, the limited hypothesis as to their aetiology, in which only vitamines are taken into account, will have to be extended so as to include not only other elements of nutrition but also the general metabolism.

One point, which has come most prominently before my mind as the work has progressed, is the unity of a complete diet and the interdependence of the dietetic elements. This might have been expected. Knowledge has been accumulating in recent years which emphasises the importance of balanced diets, and we know that to cut out one element of the diet means not only the absence of that element, but also the ineffective action of other elements. For instance, when carbohydrates are removed from the diet, fat is

ineffectively oxidized, and there is also good evidence that in their absence animals and plants are incapable of synthesizing proteins from the amino acids. This is a simple instance of the absence of one element upsetting the action of other elements. When carbohydrates are given in large excess we know from the investigations of Bloch (33) on the diets of children in Denmark during the war the dire results that may ensue. When protein is cut out of the diet, although the direct and immediate effects of its absence are not properly understood, yet both man and animal are incapable of eating the diet for more than a few days. Not only does this inter-relationship hold between different elements of the diet, but also between these elements and the general metabolism of the body. For instance, however much fat there may be in the diet of an animal living in extreme cold, great discomfort is experienced under these conditions unless there is also a large amount of protein. Whereas fat is desirable and eaten with satisfaction where cold and exposure are to be endured, it is generally nauseous to those confined or living in a hot or sultry climate.

These few instances cannot fail to impress the investigator of dietetic diseases that any problem, which at first sight appears limited, may ultimately have to include a consideration of other factors in addition to the one that at first appeared all important. It has so happened in this investigation.

While it is evident that a vitamine, probably Fat-soluble A, occupies a position of prime importance in the aetiology of rickets, it is undoubted that this vitamine works in a close relationship with the other dietetic elements, and, moreover, with the general activity of the body, so that all the other factors both of diet and environment must be analysed in relation to it.

There is one other fundamental difficulty in investigations of this type, in that the facts observed are expected to explain the production of a disease in a type of animal different from that upon which the experiments are made. This difficulty holds in all animal experimental work and the danger of arguing from one animal to another cannot be emphasized too strongly, more especially in dealing with questions of diet. If, for instance, the work on scurvy had been attempted on rats instead of guinea-pigs, no progress could have been made, for these animals do not develop the disease. That is to say the human being, guinea-pig, and rat react differently to the absence of the anti-scorbutic factor. Again it will be seen that while the resemblance between the anti-rachitic factor and Fat-soluble A is so similar as to warrant the suggestion that they are the same things, yet the evidence is not complete. The apparent difference may, of course, be due to the difference of the metabolism of the rat upon which the experiments involving the distribution of Fat-soluble A have been made, and the puppy which has been the experimental animal in this work on rickets. It is not likely that the difference between a puppy and an infant is as great as that between a rat or guinea-pig and an infant, yet caution is necessary in applying the results of puppy experiments to the problem of rickets in children.

In addition to the solution of the practical problem of rickets, one other object has been constantly before my mind since it

became evident that a vitamine was bound up in the aetiology of this disease. Our knowledge of vitamines has up to the present depended upon work somewhat limited both in its nature and the number of species of animals investigated, and it was hoped that the use of the dog would not only lead to results more directly applicable to the human being, but also would afford a wider basis for considering the part played by these substances in general nutrition.

This research has centred round calcium metabolism because it is the one object upon which all experimental work on rickets can be focused with the certain knowledge that a solution of the problem will clear up the practical problem of rickets as a disease. A large amount of German research has been carried out with the idea that a deficient calcium intake alone is responsible for rickets. Even now this hypothesis meets with strong support but it will be generally admitted that experimental results on animals and clinical experience are opposed to calcium deficiency as being the main cause of rickets. The problem of deficient intake of calcium has received comparatively little consideration in this research. A sufficiency of calcium has been given in most diets, an amount, that is to say, which will afford the opportunity for the formation of abundant good bone if the other conditions are satisfactory. Whether the body can make full use of the calcium depends on several circumstances and the study of these determining circumstances forms the basis of this investigation.

The material accumulated in this research is great and much of it, especially on the histological side, awaits closer examination. In the course of the work, facts bearing on other diseases have become evident and these, when more completely developed, will be published elsewhere.

II. METHODS OF EXAMINATION

Various methods have been employed for diagnosing and estimating the degree of severity of the rachitic condition, and it is necessary to discuss these methods, more particularly because it is sometimes difficult to correlate the results obtained by the different methods. It is true that as a general rule, a puppy, having the appearance of advanced rickets, will show on radiographic and histological examination typical signs at the ends of the long bones together with the production of osteoid tissue. In addition, also, the calcium content of the bones will be very low. On the other hand, it sometimes happens that the calcium content of the bones may be low when at no stage of the experiment have the external appearance or radiographic results revealed bad rickets. Very occasionally in such cases, there may have been but small external indications of the disease. The chief characteristic of rickets is the defective laying on of calcium salts in the growing bones. This has been emphasized by Pommer (3), Schmorl (4), and other German investigators. This poverty in calcium is revealed by all the methods of examination, but in different ways and at different stages of the

disease, so that each method has its advantages. Absence of or deficiency in calcium salts may be the outcome of many pathological conditions in addition to rickets, such as osteomalacia, pseudorachitic osteoporosis, scurvy, &c., and, although the pathological anatomy of these diseases is still obscure, there is sufficient knowledge accumulated about rickets to place the histological method of examination in a position of supremacy.

The following methods have been used for identifying the rachitic condition :

    (1) External appearance.
    (2) Radiographic examination of the bones during life.
    (3) Histological appearance of the bones.
    (4) Calcium content of the shafts of the bones.

(a) External Appearance.

The appearance of rickets in a dog (Fig. 2) is comparable to that of a rachitic child (Fig. 1). The swollen epiphyseal ends of the bones are unmistakable, more particularly at the growing ends of the radius and ulna. This swelling can be well seen in Fig. 2, which is a photograph of a retriever with rickets. The costochondral junctions also enlarge and, if the dog has a smooth coat, its rickety rosary can often be easily seen. In this work, however, but little reliance has been placed on the swelling of the costochondral junctions, for it has been found to be so variable from animal to animal. A large quickly growing puppy nearly always has more prominent junctions in this position even in a normal state. In other cases, the swelling may be more developed on the inside of the chest, and can only be appreciated after death, although the animal is really rachitic. In very bad cases the costochondral junctions may be drawn in, giving the chest a very deformed appearance. Again, the abdomen is usually prominent in rachitic dogs, and a sulcus corresponding with the well-known Harrison's sulcus of a child is sometimes seen.

As in children, the animal often becomes more lethargic and listless as the rachitic changes develop. The intense interest of the normal healthy puppy in all its surroundings disappears to a large extent, and there is great diminution in its small movements. Often the animal loses its desire to bark, and in this respect resembles a ' good ' child with rickets. The muscles are flabby and are unable to contract to allow the animal to run quickly. Long before the bone changes are sufficiently severe to be an impediment the animal may be incapable of running at any speed. Sometimes the effort to run is lamentable, although the appearance of the puppy would not lead any one to suspect this disability. The power to run has often been used by me to test the relative development of the disease in various members of an experimental series, and, although the method is crude, it is sometimes possible to state with reasonable accuracy how the experiment is proceeding.

The ligaments of rachitic puppies often become slack and this exaggerates greatly the appearance of bending of the legs. Occasionally this happens a week or two after the beginning of the experiment, before any rickets can have developed, and, at that time, such

a change is very misleading. At these early periods I doubt whether it has anything to do with rickets, and it can often be traced to the animal getting wet when very young, and it may appear in animals closely confined. When the ligaments give in this way, often in one leg only, it is impossible to compare the animal affected with the other puppies in the series, as the puppy may be incapable of movement. In the later stage, when the disease is fully developed, the ligaments generally slacken, but then it may be regarded as a more natural rachitic change and is in keeping with the rachitic syndrome. When the disease is fully developed, the bones bend because of their softness due to deficiency in calcium salts. The amount of bending depends not only on the softness of the bones but also on the weight of the animal. The heavier the animal, the more bending will be evident, so that in the case of small light animals there may be little or no bending although rickets is present.

(b) Radiographic Examination of the Bones.

This is an excellent method for following up the development of and recovery from the disease. For a large period of this research it has been customary to radiograph the wrist joint of each puppy at intervals. Changes are seen in the first place at the growing ends of the bones. Often the first indication of rickets is seen in changes in shape of the epiphyseal end of the diaphysis of the ulna. This in normal growth is pointed and ought to fit closely into the corresponding depression of the ulna epiphysis when this is formed. With the development of slight rickets the end becomes more or less rounded, and, when more severe, flat or even concave. These changes can be seen in many of the radiographs which are illustrated in this paper. The flattening of the growing end of bone is the earliest and most sensitive change that can be readily observed. With this flattening the amount of tissue easily pervious to the X-rays and containing deficient calcium between the epiphysis and diaphysis increases. The broader this band of non-calcified tissue the worse is the rickets.

On close examination of the growing edge of cartilage it will often be seen that it has a wavy and indefinite outline in rickets, whereas in the normal animal it is straight and thin. If the disease has started in the puppies at an early age there may be delay in the ossification of the epiphyses. The growing end of a bone in a normal puppy is highly calcified and is more impervious to the rays, so that it generally stands out in sharp contrast to the rest of the bone. In slight cases there may be no other indication of rickets than the absence of this more intense calcification. This point is well seen in Figs. 52 and 54. In Fig. 52 the puppy had had cod-liver oil as its fat, and in Fig. 54 pea-nut oil had been eaten. In neither radiograph would rickets be diagnosed by the ordinary tests of increased zones of uncalcified tissue. It can be easily seen, however, that there is a difference in the intensity of the calcification processes going on in the newly-formed calcified tissue. In Fig. 54 (pea-nut oil) there is no band of increased calcification at the growing end, whereas the cod-liver puppy, Fig. 52, shows this in good contrast. Calcification is more intense in the cod-liver than in the pea-nut oil puppy.

In more advanced cases of rickets, instead of the calcified matrix

appearing in the radiograph as parallel bands at right angles to the growing cartilage, it is irregular and sometimes granular.

Another difference between the normal and rachitic bone is seen in the thickness of the calcified periosteal bone, this difference being more prominent when the experiment has continued for more than three months. It is often very striking and may sometimes appear at an early stage. The calcified periosteal bone in rickets is often thinner, thus giving the appearance of an enlarged medullary cavity. This difference in the amount of compact bone under the periosteum can be seen in Figs. 128 and 129 and in many of the radiographs. If the rachitic diet is only started after the puppy is three or four months old, no epiphyseal changes of note may be evident on radiographic examination. In these cases, however, the difference in the thickness of the periosteal bone between the normal and rachitic animal will stand out prominently.

The question of the size of the medullary cavity is an interesting one. It is certainly often increased because of the thinness of the periosteal bone, but, apart from this, it will usually be found to be abnormally large. The rachitic bone is generally broader, and no doubt some part of this increased diameter of the medullary cavity is due to rickets. On the other hand puppies with the normally broader bones seem to develop rickets more easily—generally, no doubt, because they belong to bigger and more rapidly growing dogs. But it is difficult to say precisely how much of the increased diameter is due to rickets and to what extent the rickets is more intense because of the broader bones. This enlarged medullary cavity and the deficiency in periosteal compact bone may remain throughout the life of the animal even after recovery from the disease, although on recovery the medullary cavity especially at the ends of the bone becomes smaller in diameter (see Exp. 192). In Figs. 91 and 99 can be seen the great contrast in the size of the cavities of bones in a normal (Fig. 91) as compared with the bones of what at one time was a rickety dog, which recovered later on change of diet (Fig. 99). The difference in the amount of compact bone in these cases is also evident. In each case the animal was full grown when the radiographs were taken. It will also be noticed how with recovery the epiphyseal swelling at the growing end diminishes in size and the shaft-ends become thinner (Figs. 97–9).

(c) The Calcium Content of Bones.

It has been usual to estimate the calcium in the shafts of the femurs of each experimental animal, as long a piece of the shaft being taken as possible in each case. The method used for estimating the calcium was that described by Cahen and Hurtley (7). The bone was weighed immediately on being cut out, the muscle, &c., attached to it having been dissected off. This weight is that of the ' fresh bone '. It was then heated at 105° to 110° C. for about eight hours until the water was driven off and weighed again. The second weight is that of the ' dry bone '. Many of the results are given as percentage CaO in the fresh and dry bones. It will be seen on examining the figures that sometimes there is a discrepancy between the results, the calcium percentage in the dry bone appearing high when

the corresponding percentage in the fresh bone is low. This discrepancy can often be explained. In some cases the animals have gone off their food and lost weight continuously for a time before being killed. When this happens, the marrow fat diminishes and often disappears entirely. When the bone is weighed in the fresh condition, the medullary cavity, instead of containing fat as it usually does, is full of blood or other tissue fluids. When dried, this fluid evaporates, but drying does not get rid of the fat, so that, whereas the former bone loses a lot of weight by drying, the latter loses much less. Consequently, when there is no marrow fat, the percentage CaO in the fresh bone may be very low, but when reckoned in terms of the dry bone it will be much higher. It is clear that the percentage CaO content of the fresh bone is the more reliable figure for comparative purposes.

The calcium content of the bones is a useful indication of the intensity of rickets when controlled by histological and radiographic methods, but it is necessary to remember that the figures cannot be used indiscriminately and several points of importance must be considered.

(1) The percentage amount of calcium in the shaft of a bone depends, even in normal dogs, on the age and breed of the animal. A young animal of, say, four months old may only have about 11 per cent. CaO in the fresh bone, whereas at six months the percentage may be 14 to 16. The percentage CaO in the fresh bone of an adult dog is 24 or more. In comparing figures, therefore, the animals ought to be of similar age. It is obvious that the longer the experiment continues, the greater will be the difference in calcium content between normal and rachitic dogs.

(2) The wider the medullary cavity and the greater the cross section of the bone, the lower will be the calcium percentage content. It has been pointed out above that rickets is more frequently associated with dogs having bones with wide medullary cavities, but it cannot be accepted that all this widening is due to rickets, because the disease appears to attack more readily those puppies, even in the same family, with the broader bones. The broader the bone the greater is the amount of calcification necessary to keep the growth normal. In using the calcium results, therefore, as a measure of rickets, this difference in the cross section of bones must remain a difficulty, and it can only be surmounted by having the dogs as similar as possible in comparative experiments and, even then, by not arguing too precisely from small differences in results. As a general rule, the differences in calcium content of normal and rachitic dogs is so great, more especially if the experiment has continued over a period of four months or more, that the question of size of bone is of small importance, but, in the more refined experiments where small differences are being examined, it is a point worth due consideration.

(d) Histological Examination of Bones.

Schmorl (4) states that only those experimental results on rickets in animals are worth consideration when the chemical examination of the bones is controlled by a knowledge of their pathological anatomy. With this I agree, although there appears to be no

definite views as to what is the true histological appearance of rachitic bones in dogs. That there must be some difference between human and canine rickets from the point of view of minute anatomy is certain, even if only because of the difference in the time relations of the disease in the two types of animals. According to my experimental results, to produce typical rickets in hitherto normal puppies the treatment ought to start in the first three months of life. In children typical rickets does not often develop after the age of three or four years, and is generally found under the age of two.

Many of the changes observed at the epiphyseal ends of bones in rickets can be produced experimentally in puppies by other conditions than those conducive to rickets. The hypertrophy of the proliferating cartilage, the invasion of the cartilage by marrow vessels, the absence of calcification at the cartilage-bone zone can also be produced by deprivation of calcium salts and by feeding with phosphate-poor food (Heubner (8)). The other histological appearances are not, however, the same as in rickets, so it is evident that no reliability can be placed on the histological appearance of endochondral ossification as the final test of rickets, although as in the case of children, these changes at the epiphyseal ends are a useful guide. According to Schmorl (4), endochondral changes similar to those seen in rickets can also be produced in man by syphilis, Barlow's disease, and traumatic separation of the epiphysis. Since radiographic examination reveals for the most part changes of calcification at the epiphyses, the above facts make its limitations obvious. As most of the figures given in this publication are radiographs, it is necessary to add that the experiments have been controlled histologically and chemically.

The presence of osteoid tissue is the crucial test of rickets in children as first pointed out by Pommer (3). When, therefore, excess of osteoid tissue is found in puppies' bones, until the subject of rickets in dogs has been more completely worked out, it must be accepted that a rachitic condition is present, even when there are other complicating bone changes. When Dibbelt (9) produced an excess of osteoid tissue in the bones of puppies fed on horse flesh and carbohydrate, Schmorl describes it as ' etwas Akzidentelles ' because there were also present osteoporosis and abundant osteoblasts lying on the osteoid layers. In addition also there was evidence of abnormally great bone absorption in the excessive number of osteoclasts. There would appear to be no great difficulty in imagining a combination of rickets and osteoporosis as the diagnosis of the condition produced by Dibbelt.

Many histological methods have been used in this research for demonstrating the presence of osteoid tissue.

These include

1. Fixing and partially decalcifying in Müller's fluid and subsequently staining
    (a) in ammonia carmine (Pommer). Figs. 123, 124.
    (b) in silver nitrate and eosin. Figs. 125, 126, 127.
    (c) in methylene blue and eosin.

2. Schmorl's thionin method. Fig. 122.

3. Weil's method, which consists in fixing the tissue in mercuric chloride, staining with borax carmine, impregnating in balsam, and grinding down the section. The bone is not decalcified by this method. Figs. 118, 119.

4. Cutting small pieces of bone—not previously decalcified—and staining by various methods. The silver nitrate-eosin staining method gives good results.

Microphotographs of bones stained by these various methods are shown in Figs. 114–27.

When there is osteoid tissue present, it will usually be found that the calcified bone of the trabeculae is also imperfectly formed. The cells of this imperfect bone are swollen, irregularly placed, and sometimes scarce, and are in striking contrast to the cells of true bone which have a squeezed appearance and are more regularly arranged. These differences are evident whatever method of preparation and staining is adopted. (Compare microphotographs, Figs. 120 and 121.) The fibrillar appearance of osteoid tissue can also be seen (Fig. 124).

Macroscopically also osteoid tissue can often be easily recognized especially in advanced rickets. It will be found in such cases that the compact bone forming the lamellae of the skull bones is thick and soft and cuts easily with a scalpel. Sometimes the bones are so soft that they can be bent with the fingers.

As regards the possibility that the pathological condition produced in the puppies is pseudo-rachitic osteoporosis or that this condition is a complicating factor, it may be stated that osteoporosis is not often a feature of the bones. In one or two experiments where the effect of acidic caseinogen was tested, there was some osteoporosis in addition to rickets. These were exceptional cases. Osteoporosis would not be expected as the puppies received a good supply of calcium salts in their diet.

The number of osteoblasts and osteoclasts indicating the extent of laying down and absorption of bone varied greatly in different experiments, but in general there was a great diminution of these cells in the bones of rachitic animals. On the other hand, even without any advanced rachitic development, cessation of growth may be accompanied by a striking diminution of these cells (Exp. 300). In another member of the same group (Exp. 299) where the growth was vigorous but rickets not pronounced, the osteoblastic and osteoclastic activity was very great.

The pathological anatomy of rickets as it appears in the puppies of this experimental work may be said to be strictly comparable to that met with in human rickets in so far as the histological appearance of the endochondral ossification is concerned. There is also abundant osteoid tissue present while osteoporosis, except in certain cases, is absent. Again, in most of the experiments the incidence of rickets is associated with diminished osteoblastic and osteoclastic activity.

Although I have no doubt that the condition developed in the puppies is comparable to rickets in children, I agree with Schmorl's plea that it is essential that the pathological anatomy of the bones of animals should be closely reviewed, because there are so many different factors capable of influencing the formation of bone. To

me the subject is one of extraordinary difficulty, and I should like to acknowledge the assistance I have received from Professor S. G. Shattock in considering this side of the work.

(e) General Consideration of Methods.

I have stated above that, although on the whole there is general agreement between the results obtained by the various methods employed in this research, yet there are occasions when this is not so. For instance, in a few cases the calcium content of the bones would point to very pronounced rickets and yet the radio-graphic and histological results indicate that at no period of the experiment has the disease been advanced. Some part of this disagreement can be explained. In puppies, the rachitic symptoms of enlarged epiphyses and the changes associated with this enlargement which can be detected by radiographic and histological methods, develop only in young animals under the conditions tested in this research. If the experiments begin when the puppies are at least 3–4 months old no obvious rickets may develop. If, however, the dietetic conditions conducive to rickets be maintained in these older animals, although the usual outward signs of rickets are absent, it will be found that calcification of the shafts of the bones is defective, a fact which can be detected by the radiograph and better still by determining the calcium content of the bone shafts. In any particular animal therefore, if the diet has only slight rickets-producing effect, the animal may tide over the earlier part of the experimental rickets and escape enlarged epiphyses and other gross changes of endochondral ossification. That, however, the growth changes in the bones are not normal can be seen when the calcium in the bone shaft is estimated and found to be much below the control. Several instances in the course of this work have been met with where the rachitic symptoms have appeared small and at the same time the calcification processes have been defective. In Figs. 128 and 129 is seen the relative thickness of the periosteal bones when cod-liver oil and rape-seed oil were eaten. Neither puppy had rickets at death according to the radiographs but there is a great difference in the thickness of the bone and in the histological picture.

On the whole the radiographic method is valuable for detecting rickets, especially in the earlier stages, but there are occasions when it fails, together with the deductions made from external appearance. In all these cases, the calcium content of the bone shaft in addition to the minute anatomy give useful information as to the failure or success of the experimental methods employed in producing abnormal or normal bone. I wish to emphasize that the swollen epiphyses and the apparent excessive production of tissue at the growing ends is a process which takes place in the younger puppies, whereas a deficiency in calcification is a process which may continue over a long time, probably in fact for the whole period of bone growth.

The importance of these facts can be readily seen as they apply to man. Babies under two are specially liable to rickets and after this age the disease in an active form is much rarer. This does not

mean that calcification processes in bones and teeth in later years are necessarily normal.[1] The comparative rareness of the classical signs of rickets in children over two years of age is very misleading and it cannot be too strongly emphasized that in spite of their normal appearance, the formation of the bony tissues may be extraordinarily defective so long as growth continues.

This point has a still greater significance when it is remembered that the calcification of the teeth is wrapped up with the question of rickets and that the complete elimination of the latter would go a long way to settling the problem of defective teeth in civilized man. This investigation on the teeth is being worked out by May Mellanby (10), who has already shown that perfect and imperfect calcification of the teeth is a nearly related problem to similar changes in the bones.

While, therefore, I would be the first to admit that rickets is not alone a deranged calcification of bones, as an objective method of study the chemical method presents the advantages of quantitative measure lacking in the histological and radiographic methods.

It is evident that the calcification processes of bones can be deranged by many other causes than those responsible for rickets, and that to place too much weight on the calcium content may lead away from the particular disease and involve the investigator in a worse morass than rickets itself. This can only be met by constant control of the experimental conditions and the use of histological methods. It is true that, in some of the earliest experiments, the rachitic changes were possibly associated with scurvy but, in all the later experiments upon which I place most reliance, orange juice has formed an element of the diet. The fact that I hardly ever see any indication of pain in the most rickety puppies is evidence that scurvy has been eliminated.

The further danger of mixing up rickets and pseudo-rachitic osteoporosis has already been dealt with.

III. EARLIER EXPERIMENTS

Anybody familiar with the large number of hypotheses that have been advanced to explain the aetiology of rickets, must be aware of the difficulties under which the beginning of a new investigation of this disease is made.

The only outstanding and definite idea at the commencement was the necessity of carrying on the experiments with animals capable of developing the disease. For it is a commonplace that this experimental method offers the best means for making definite advance. We have seen for instance that Eijkmann's (11) discovery of ' poly-neuritis gallinarum ' was the beginning of the investigations which ultimately led to the solution of the ' beri-beri ' problem. Holst and Fröhlich's (12) work on scurvy in guinea-pigs quickly

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[1] In this connexion it is well to remember that of 99 children who died between the ages of 2 and 4 years, and whose bones were examined histologically by Schmorl (4), 81 showed signs of rickets. In 15 of these cases the disease was active, in 17 healing, and in 49 healed.

brought to light the aetiology of scurvy in man and placed that disease on a definite scientific basis.

There was, therefore, reasonable certainty that, if the conditions under which an experimental animal develops rickets could be found, the problem would then be fairly accurately defined and made easier. Fortunately the experimental animal was ready to hand, for it has long been recognized that puppies develop rickets. What to do with the puppies in order to produce the disease was unknown to me, because all the hypotheses that have been advanced to explain rickets in children could likewise be offered in explanation of a similar disease in puppies.

At the beginning of this investigation a hypothesis discussed by clinicians was that depending upon the work of Findlay (13) in which he showed that confined puppies developed rickets while other puppies living on the same diet, when allowed exercise, remained normal. According to Findlay the disease of rickets in children could be explained by deficiency of exercise. Experiments, which will be described later in the paper, were prepared in order to test the exercise hypothesis. It was soon evident that, although exercise might be a factor of importance, yet it could not be the primary factor responsible for the disease. It was shown, for instance, that puppies could be confined under very close conditions and yet, if well fed during this period, the disease did not develop. Exp. 198, Figs. 89 and 90; Exp. 350, Fig. 113.

In order to get a line for research a large number of preliminary experiments were carried out with the object of testing various hypotheses, experiments many of which gave no result worth following up. It seemed for instance that reduced oxidation changes in the animal's body might play an important part in the development of the disease. On this basis attempts were made to produce local changes in bones as seen in rickets by, for instance, removing or tying the lymphatic vessels of one limb. It was thought that a local operation of this sort which would interfere with the removal of waste products from the limb, might at the same time reduce the oxidation changes in this way. All the experiments performed on these lines were negative in their results.

In other experiments performed with the same object the attempt was made to produce lymphatic stasis more or less complete throughout the body by tying the thoracic duct just as it enters the venous circulation. In these experiments no rachitic changes resulted that could definitely be ascribed to the cessation of lymph flow.

Again, in order to reduce processes of oxidation, quinine was given to other puppies. These experiments also led to no positive results.

During the course of the above-mentioned work, experiments of a tentative nature were being carried out to see how the disease could be effected by diet. In the first experiment made, a puppy was fed on boiled horse flesh without fat. After about ten weeks of this diet the animal developed a rickety appearance. It seemed certain, however, from the general condition of the animal that scurvy was associated with rickets. There was, for instance, obvious pain in walking. After being anaesthetized, the diagnosis of scurvy

was made certain by the haemorrhages present. It was found at this time that if puppies, in addition to the meat, received a substantial quantity of milk each day, they remained in good health.

While testing the effect of varying salts in the diet, a mixture consisting of milk and equal parts of oatmeal and rice was used as the basal diet because of its low sodium content. It was found that on a diet of oatmeal, rice, and milk puppies ultimately developed rickets when the milk was limited to about 200 c.c. per diem. The addition of sodium chloride did not influence the development of the condition. The addition, on the other hand, of a small quantity of potassium chloride resulted in severe malnutrition and death.

A large number of experiments were made in which this diet of milk, oatmeal, and rice was used as the standard and, in all cases under laboratory conditions, the animals developed rickets. The treatment which prevented the disease was an increase in milk consumption to, say, $\frac{1}{2}$ litre a day. When the oatmeal and rice were replaced by ordinary white bread, other conditions being the same, rickets also developed.

The drawback to the use of this diet was that the period necessary for the production of the disease was long, often 4–6 months, and, except in puppies of a large rapidly-growing type, the bony changes and other symptoms were not as strongly developed as was desirable from an experimental point of view.

The natural question that arose at this stage was, what was the factor associated with the large milk intake that prevented the development of rickets ? The answer that suggested itself, as may well be imagined in consequence of the results obtained by Bland Sutton on the effect of cod-liver oil when given to young lions in the Zoo, was that the fat of milk contained some inhibitory factor. It appeared in other words as if the explanation of rickets was to be found in the theory that a deficient fat intake was the main responsible factor.

In order to test this point the fat of the milk was removed by skimming, and it was noticed that the animals developed rickets more rapidly. At this stage of the work a concoction called ' Marylebone cream ' was being distributed in the Infant Welfare Centres in London as a curative agent for rickets. ' Marylebone cream ' was then an emulsion of linseed oil, and as a matter of interest the effect of linseed oil on the development of the disease was tested. The cream was removed from the milk by skimming and replaced by an equivalent quantity of linseed oil, and it was soon discovered that linseed oil did not possess the anti-rachitic effect as did the milk fat.

Before this period McCollum's (14) work on the distribution of Fat-soluble A vitamine was published. The results of experiments carried out with linseed oil as opposed to butter naturally led to the suggestion that the Fat-soluble A vitamine played some part in the aetiology of the disease.

It seemed advisable to investigate the action of the other two vitamines, viz. the water-soluble and the anti-scorbutic, on rickets. In order to test the effect of the water-soluble vitamine, yeast was added to a diet of milk, bread, and linseed oil (in these early experiments

B

the milk was only skimmed and not separated). The effect of adding the yeast was that the animals appeared to thrive better, but there was quite obviously no anti-rachitic effect, that is to say, the water-soluble factor had no influence in preventing rickets. In other experiments the effect of the anti-scorbutic vitamine was tested. To a diet of milk, bread, yeast, and linseed oil, the juice of a quarter of an orange daily was added. The addition of the orange juice again seemed beneficial for the general health of the animals but once more did not prevent the development of the disease. It was in fact evident that the deficiency of anti-scorbutic and anti-beri-beri factors did not explain the aetiology of rickets.

Large numbers of experiments were carried out in the endeavour to determine the part played by other dietetic factors. For instance, to a diet of bread and limited milk, substances like malt extract, cod-liver oil, and other forms of fats such as suet, pea-nut, coco-nut oil, and cotton-seed oils, also meat protein, meat extract, casein, were added and their effect on the development of rickets tested.

These early experiments were crude, but the results were more or less in keeping with those obtained by the later more refined methods. For instance, cod-liver oil and suet had pronounced anti-rachitic action, meat also had a preventive effect to some extent, and malt extract had an anti-rachitic action when eaten in large quantities. Quantities less than 20 c.c. a day appeared only to have slight inhibitory effect. Some of these earlier results have been published (1).

It may be of interest to add that the experimental work had continued for about two years before good evidence of differences in the anti-rachitic action of fats was obtained.

IV. THE EFFECT OF DIET ON THE PRODUCTION OF RICKETS

(a) The Effect of Various Oils and Fats on the Development of Rickets.

We have seen in the foregoing section how the earlier work led step by step to the evolution of a diet which produced rapid and marked rickets in well growing puppies. This diet consisted of :

> Bread *ad lib.*
> Separated milk 175 to 250 c.c.
> Yeast 5 to 10 grm.
> Orange juice 5 c.c.
> Sodium chloride 1 to 2 grm.
> Linseed oil 10 c.c.

I now propose to deal with the effects of other oils, and to describe the experimental work, upon which is based my previously published deduction, that there is great difference in the anti-rachitic effect of the different oils tested. When alluding to this part of the work in previous publications, I have insisted that the classification of fats into a definite order as to the amount of anti-rachitic factor present in each, must be of a tentative nature. This is not because

of the lack of work on the point, but because of the great difficulty of carrying out quantitative experiments so as to give definite and precise information. Facts of this nature are only brought to light by working on animals of definite age, size, rate of growth and breed, keeping all factors in the diet except the fat constant.

In the earlier experiments on the action of fats in rickets, I had not recognized that the amount of bread eaten by the puppies was a crucial point. Up to this time all factors in the diet were controlled except the bread, which was varied according to the appetite of the animal. This fact deprives the earlier work of some of its quantitative accuracy. Nevertheless, definite results were obtained which agreed, in the main, with the experimental results obtained later when all the elements of the diet were eaten quantitatively.

Even with full knowledge as to the conditions which must regulate these experiments, it is very difficult to carry out perfectly a comparable series. The puppies will probably eat their food for ten weeks or so. Then the defective diets begin to have a real influence on the health of the animals, and one by one they leave some food uneaten. If the experimenter decides to get a result at this stage by radiograph, then the animals will have to be anaesthetized, and this procedure will increase the number of puppies not completely finishing their diets. I shall discuss elsewhere this difficulty of recovery from anaesthesia in the case of dogs on deficient diets, as it is apparently a point of practical importance (p. 72).

Up to the present, when dealing with different fats I have not succeeded in getting a completely satisfactory quantitative experimental series beyond about the eleventh week of dieting. At the end of this period, radiographic and histological differences are well brought out, but in order to obtain good differences in the calcium content of the shafts of the bones, the experiments ought to continue for fourteen weeks or longer. In spite of these difficulties, a fair nsight has been obtained as to the relative anti-rachitic power of the various fats, but there is still need for much work on the subject. There is great variation in method of manufacture of oils and fats, even from the same type of seed, and there remains the problem of ascertaining the effect of the manufacturing processes on the anti-rachitic vitamine. Speaking generally, however, this difficulty has not led to the great variation in results that might have been expected, possibly because the types of oil examined have been of the same standard. In the first experiments olive oil appeared to hold a higher position in content of anti-rachitic vitamine than was obvious in later experiments, but this difference must, I think, have been due to the smaller amount of bread eaten.

In most of the later series of experiments, meat was put into the diet in order to induce the puppies to eat up completely each day's ration. This plan ensures more uniform results in comparable experiments, but has the drawback of reducing the rachitic changes. It is a question of choice between producing very bad rickets but less uniformity for comparison and more uniformity and less rickets.

I shall now proceed to give an account of some of the numerous

experiments on fats that have been carried out. Unless otherwise stated, the animals in each series belonged to the same family.

In referring to the histological condition of the bones ' slight rickets ' means less abnormality than ' some rickets ', and both of these less than ' rickets '.

COMPARISON BETWEEN LINSEED, BUTTER, OLIVE, AND COD-LIVER OILS.

General Diet :

Bread *ad lib.*
Yeast 10 grm.
Separated milk 175 c.c.

Age at commencement, 8 weeks.

No. of experi- ment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results
		weeks.	grm.	grm.	grm.	%	%	
145	+ linseed oil, 10 c.c.	17	1,830	3 605	1.775	21·60	12·35	Rickets
146	+ butter, 10 grm. .	17	1,920	3,765	1,845	26·95	15·89	Normal
147	+ olive oil, 10 c.c. .	17	1,445	2,645	1,180	23·79	13·22	Some rickets.
148	+ cod-liver oil, 10 c.c.	17	1,735	3,890	2.155	27·78	16·51	Normal.

These puppies were wire-haired terriers of a slowly growing type. The histological examination showed that only one, viz. 145, the linseed oil puppy, had well-developed rickets ; 147, olive oil had some rickets, whereas 148, cod liver oil, and 146, butter, were normal. It is interesting to note, what has been corroborated throughout, that cod-liver oil is better than butter. In these experiments the cod-liver oil dog has a higher percentage of calcium in the shaft of the femur than the dog which had butter. Another point to note about this particular experiment is that the cod-liver oil dog grew most rapidly and the olive oil dog the least rapidly. This difference was largely due to the better appetite of cod-liver oil dog, so that it ate more bread. The olive oil puppy ate least bread and this is probably the reason why it only developed slight rickets (see p. 42). The cod-liver oil puppy, on the other hand, remained normal in spite of eating most bread. Note also the comparatively good growth of 145 on the linseed oil. According to accepted teachings the diet eaten must have contained a minimum of Fat-soluble A, and in spite of this deficiency, good growth resulted.

COMPARISON BETWEEN LINSEED AND COD-LIVER OILS.

General Diet :

Bread *ad lib.*   Salt 1 grm.
Yeast 5 grm.   Separated milk 175 to 250 c.c.
Orange juice 3 c.c.   Meat 10 grm.

Puppies—cross between collie and terrier. 9 weeks old at commencement of experiment.

General Diet with Various Oils.

No of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Weight after 3 mths. of diet.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
176	+ linseed oil, 10 c.c. . + 175 c.c. sep. milk .	18	1,705	2,805	5,035	—	7·68	Bad rickets.
177	+ 10 c.c. linseed oil .	18	1,360	2,590	4,155	—	9·56	Bad rickets.
178	+ cod-liver oil, 5– 7·5 c.c.	18	1,750	5,525	4,250	—	12·5	Practically normal.
179	+ cod-liver oil, 10– 15 c.c.	23	1,910	6,140	4,325	—	13	Normal.

The difference in the calcium content of bones in these dogs is striking, and is in conformity with the rickety appearance of 176 and 177 and the normal appearance of 178 and 179. That is to say the linseed oil puppies developed bad rickets, whereas the cod-liver oil animals remained normal, even in the case of 178, where the oil eaten was only 5 to 7·5 c.c. per diem. Notice also that 176, which received as much as 350 c.c. of separated milk each day, developed bad rickets. Both the rachitic animals 176 and 177 became ill and lost a great deal of weight during the last three weeks of the experiment. The radiographic appearance of the wrist-joint of these puppies are shown in Figs. 3, 4, 5, 6. Needless to say, all conditions other than those described were constant, and it is difficult to believe that any factor other than differences in the oil eaten could have been responsible for the great difference in the results obtained.

COMPARISON BETWEEN OLIVE, LINSEED, COTTON-SEED, BABASSU, PEA-NUT, AND COD-LIVER OILS.

General Diet :

Bread *ad lib.*	Orange juice 3 c.c.
Yeast 5 grm.	Separated milk 175 to 250 c.c.
Salt 1 grm.	No meat in diet.

Animals 6 weeks old at the start of the experiment.

General Diet with Various Oils.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
185	+ olive oil, 10 c.c. .	7	1,495	2,500	1,005	—	7·3	Slight rickets (7 wks.).
186	+ linseed oil, 10 c.c. .	7	1,325	2,470	1,145	—	6	Rickets (7 ,,).
187	+ cotton-seed oil, 10 c.c. . . .	16	1,335	1,900 Max. after 9 weeks, 2,750	?	—	7·6	Rickets (16 ,,).
188	+ babassu oil, 10 c.c	7	1,240	1,725	485	—	6·55	Bad rickets (7 ,,).
189	+ pea-nut oil, 10 c.c.	29	1,350	4,000 Max. after 22 weeks, 5,095	—	—	9·77	Some rickets (29 ,,).
190	+ cod-liver oil, 10 c.c.	24	1,320	6,550	5,230	—	14·4	Practically normal (24 ,,).

Of these puppies 185 and 186 were killed by the anaesthetic when the X-ray photographs were taken, and 188 died of intestinal obstruction. 185, 186, 187, and 188 developed rickets at an early age. Radiographs of 186 and 187 were taken seven weeks, 189 and 190 ten weeks after the beginning of the experiment (Figs. 7, 8, 9, and 10). It will be seen that 190 is normal and that 186 and 187 are distinctly rachitic, 186 (linseed) being worse than 187 (cotton-seed), and 187 (cotton-seed) worse than 189 (pea-nut). 188, the babassu oil dog, also developed severe rickets, but the radiograph of this puppy has been mislaid. The only puppies that lived any length of time are 187 (cotton-seed), 189 (pea-nut) and 190 (cod-liver oil). As regards the anti-rachitic action of the fats, the radiographs indicate the following order :

1. Cod-liver oil.
2. Pea-nut oil.
3. Cotton-seed oil.
4. Linseed oil.
5. Babassu oil.

Weight (after 7 weeks of diet).

185	2,500 grm.	Olive oil.
186	2,470 ,,	Linseed oil.
187	2,290 ,,	Cotton-seed oil.
188	1,725 ,,	Babassu oil.
189	2,190 ,,	Pea-nut oil.
190	3,150 ,,	Cod-liver oil.

Here again the cod-liver oil puppy (190) has grown most rapidly, but even in the case of the vegetable oils, which are supposed to contain no Fat-soluble A, good growth is evident. As regards those puppies in this series whose life extended over a larger time, viz. 187, 189, and 190, it may be said that the cod-liver oil (190) remained normal throughout the experimental period, cotton seed (187) died at the end of 17 weeks having definite rickets, pea-nut oil (189) also showed slight signs of rickets in the subsequent radiographs that were taken, but these disappeared with the development of curative changes, and the dog remained in external appearance almost normal throughout.

The deductions to be made from this series of experiments, which it will be observed has been divided up into two portions, are that cod-liver oil stands by itself in its anti-rachitic action, and that of the vegetable oils, pea-nut oil is the best, cotton-seed oil next, and olive oil, babassu, and linseed oil are the worst. The results are in agreement throughout whether radiographs, histological appearances, or calcium content of the bones are taken as the measure of the development of the disease. The superiority of cod-liver oil over all other fats tried in promoting calcification of bone is in harmony with the earlier observed fact that it holds a pre-eminent position in its power to convert a metabolic negative calcium balance into a positive one. (Orgler (36), Schabad (37).)

Comparison between Suet, Lard, Butter, and Babassu Oil.

General Diet:

Bread *ad lib.*   Orange juice 3 c.c.
Yeast 5 grm.   Separated milk 200 to 250 c.c.
Salt 1 grm.   Meat 10 grm.

Terrier puppies of same family 6 weeks old at the start of experiment.

General Diet with Various Fats.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
180	+ suet, 10 grm. .	20	840	4,285	3,445	—	14·4	Normal.
181	+ lard, 10 grm. .	20	1,075	3,965	2,890	—	9·6	Slight rickets. Soft bones
182	+ butter, 10 grm.	19	1,140	5,800	4,660	—	12·5	Some rickets.
183	+ babassu oil, 10 grm.	19	1,460	2,920	—	—	6·6	Bad rickets.
				Max. after 10 weeks, 3,920				

Of this series of puppies the only one that developed obvious rickets, as far as external appearance was concerned, was 183, that is the babassu oil dog. The bones of this animal contained the least calcium and were very soft.

When the radiographs are examined some unexpected results are to be observed. It will be noticed, for instance, as regards the calcium content of the bones, that in the case of the butter dog the bones were much harder than in the case of 181, i.e. the lard puppy. Yet the radiographs taken three months after the beginning of the experiment show that the butter dog had developed obvious rickets, whereas the lard puppy showed no signs of the disease. Radiographs of 180, 181, 182, and 183, taken 14 weeks (suet 18 weeks) after the beginning of the diet, are shown, and it will be seen that 180 (suet) and 181 (lard) are normal, 182 (butter) has some rickets, and 183 (babassu oil) has very bad rickets (Figs. 11, 12, 13, and 14).

These results are of importance because of their inharmonious nature, the butter dog having hard bones and defective endochondral ossification, while the lard dog has soft bones and almost normal epiphyseal growth.

Thus it is apparently possible to get these two factors divorced from each other, although as a general rule they run side by side. The question will be further considered later, but, in the meantime, the difference in the rate of growth between the two puppies under discussion (181 and 182) may be pointed out. 181 (lard) only gained 2,890 grm. during the period in which 182 (butter) gained 4,660. The butter dog laid on a great deal of fat during the experimental period.

Palm-kernel Oil (Crushed and Extracted).

General Diet:

Bread *ad lib.*   Orange juice 5 c.c.
Separated milk 250 c.c.   Salt 1 grm.
Yeast 5 grm.   Meat 5 to 10 grm.

Puppies 7–8 weeks old at beginning of experiment.

No. of experiment.	General Diet	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Fresh.	Dry.	Radiographic results after 9 weeks.
		weeks.	grm.	grm.	grm.	%	%	
220	+ 10 grm. crushed palm-kernel oil	35	1,585	9,900	8,315	14·7	19·3	Very bad rickets.
221	+ 10 grm. crushed palm-kernel oil	35	1,100	4,760	3,660	15·6	20·0	Slight rickets.
223	+ 10 grm. extracted palm-kernel oil	35	1,050	5,000	3,950	14·6	18·0	Bad rickets

For the last six months of experiment 220 received 500 c.c. whole milk, 221 and 223 remaining on the original diet throughout. All showed curative changes.

In nine weeks 220 had developed most severe rickets (the worst form of rickets that had been met with at this stage of the work), 221 in the same period showed some slight indications of rickets, whereas 223 was fairly bad, intermediate between 220 and 221. It would appear that the differences in the condition cannot be accounted for by any difference there may be between the crushed and the extracted palm-kernel oil, because 220 on the crushed palm-kernel oil is the worst, whereas 221, eating the same oil, has the least rickets, 223 on extracted palm-kernel being intermediate between the two. The only other variable in these experiments was the amount of bread eaten. 220 was a heavier dog to begin with, ate more bread, and grew much more rapidly than either of the other two puppies. The differences in the rate of growth can be seen in Fig. 23. It is probable that the difference in initial size and the varying rate of growth explain the different degrees of severity of the disease in these three cases. This fact will be referred to elsewhere in the paper when the effect of varying the amount of bread in the diet is dealt with (p. 42).

Another point of interest concerning this particular family is the self-cure which took place in both 221 (Figs. 21, 22, 25) and 223 (Figs. 18, 19, 26), although all conditions as regards diet and environment remained constant.

220, which had the very pronounced rickets, was put on to a whole milk diet and subsequently cured, although its deformities were so bad that these were only partly improved (Figs. 15, 16, 17, and 24). It would appear from this series of experiments that palm-kernel oil is deficient in the anti-rachitic factor.

Radiographs taken after nine and thirteen weeks of the experimental diets are shown (Figs. 15, 16, 18, 19, 21, and 22).

The Effect of Heat on Cod-liver Oil.

Exp. 229, 231, 232. This experiment was made in order to test the effect of heat on the anti-rachitic action of cod-liver oil.

General Diet :

Bread ad lib.　　　　　　　　Orange juice 5 c.c.
Yeast 5 grm.　　　　　　　　Salt 1 grm.
Separated milk 250 c.c.　　　Meat 10 grm.

Puppies were a cross between half-bred spaniel and Airedale and were seven weeks old at the start of the experiment.

Confined to kennels (indoors) throughout greater part of experiment.

General Diet with Cod-liver Oil heated and unheated.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
229	+ cod-liver oil unheated, 10 c.c.	14	2,010	3,590	1,580	24·3	12·3	Normal
231	+ heated 4 hours at 120° C., 10 c.c.	16	2,710	5,380	2,670	21·4	10·4	,,
232	+ heated 2 hours at 120° C., 10 c.c.	16	1,675	5,000	3,325	24	12·6	,,

The radiographs taken at intervals show 229 (Fig. 27) to be normal. In 231 (Fig. 28) there is very slight flattening of the diaphyseal bone at the epiphysis after two months of the diet, whereas 232 (Fig. 29) is practically normal. It seems in fact that the cod-liver oil deteriorated to a very slight extent in so far as its anti-rachitic properties are concerned, by the prolonged heating at 120° C. for four hours, but that heating only for two hours seemed to have no effect in destroying this factor. The heating of the oil took place in a closed flask, plugged with cotton wool.

The calcium content of the bones corroborates the radiographic results, for it will be seen that in 231, where the heating went on for four hours, the calcium oxide in the fresh bone was reduced to 10·4 per cent., whereas in the other two puppies it was 12·3 per cent. and 12·6 per cent. respectively. The minute structure was normal in all cases.

The results obtained in this series are not striking, and it would be necessary to repeat the experiments under better conditions before more accurate deductions can be made. The fact that even 231 shows but slight rachitic changes makes it certain that this factor is very resistant to direct heat. Other results will be recorded later which show that in the case of butter, if oxidative changes are allowed to go on while heat is being applied, then the destruction of the factor is more rapid. 231 grew most rapidly during the earlier period, so that it is just possible that the very slight rickets that can be observed in this dog may be due not so much to the destructive action of the heat as to the more rapid growth. Radiographs of 229, 231, 232, are shown in Figs. 27, 28, and 29.

In first ten weeks of experiment :

229 increased from 2,000 to 3,600—gain 1,600 grm.
231   ,,   2,700 to 5,800— ,, 3,090 ,,
232   ,,   1,700 to 4,120— ,, 2,420 ,,

COMPARISON BETWEEN COCO-NUT OIL AND HYDROGENATED FAT.

Exp. 264, 265, 266, 267. This experiment was started when the puppies were older, i.e. when they were twelve to sixteen weeks old. They were not of the same litter.

General Diet :

Bread *ad lib.*   Orange juice 5 c.c.
Separated milk 200 c.c.   Salt 1 grm.
Meat 10 grm.

General Diet with Different Fats.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
264	+ coco-nut oil, 10 grm.	21	1,240	3,080	1,840	27·4	20	No rickets, hard bones
267	+ coco-nut oil, 10 grm.	21	4,240	5,550 Max. after 10 weeks, 6,700	1,310	26	19	No rickets, hard bones.
265	+ hydrogenated fat, 10 grm.	21	2,605	5,170	2,575	19·5	14·3	Slight rickets soft bones.
266	+ hydrogenated fat, 10 grm.	21	4,440	6,350 Max. after 10 weeks, 7,300	1,910	20	14	Slight rickets soft bones.

In keeping with the calcium results the bones of the coco-nut oil dogs were hard while those of the hydrogenated fat dogs were soft. This series of experiments illustrates that the anti-rachitic factor has a potent influence on the calcification of the periosteal bone at a time when but slight rickets can be observed at the epiphyses.

X-ray photographs of 264, 265, 266, 267, taken after seventeen weeks of the diet, are seen in Figs. 30, 31, 32, and 33. It will be seen that these radiographic results show the bones to be normal at the epiphyses. There are, however, obvious differences in the shafts of the bones as revealed by the X-rays. In the case of the hydrogenated fat dogs the medullary cavities are broader and the periosteal bone less thick.

COMPARISON BETWEEN COD-LIVER AND OLIVE OILS.

General Diet.

Bread 100 grm. Meat 5 grm.
Salt 1 grm. Separated milk 200 c.c.
Orange juice 5 c.c.

Age of puppies at beginning, seven weeks.

General Diet with Various Oils.

No. of experiment.	Diet.	Duration.	Initial weight.	Final weight Jan. 26.	Gain.	CaO in femur shaft. Dry.	Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
278	+ cod-liver oil, 10 c.c.	7	1,330	1,770	440	26·8	11·2	Normal.
279	+ olive oil, 10 c.c.	7½	1,360	1,770	410	—	8·7	Rickets.

This was a short experiment and was terminated because of an outbreak of distemper in the kennels. The radiographs showed that the animal receiving cod-liver oil (278) remained normal, while rickets was evident in 279 (olive oil).

COMPARISON BETWEEN VARIOUS OILS.

General Diet.

Bread 125 to 175 grm. Meat 10 grm.
Salt 1 grm. Separated milk 175 to 200 c.c.
Orange juice 5 c.c.

Age at beginning of experiment, eight weeks.

No. of experiment.	Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
282	+ lard, 10 grm. . .	8	2,070	3,800	1,730	20·6	7·76	Slight rickets.
283	+ suet, 10 grm. . .	9	2,170	3,880	1,710	20·0	8·4	Normal.
284	+ bacon fat, 10 grm. .	8	2,370	3,690	1,320	21·1	8·4	Slight rickets.
				Jan. 27, 4,060 (distemper)				
285	+ pea-nut oil, 10 c.c.	9	1,900	3,630	1,730	21·8	9·9	,,
287	+ olive oil, 10 c.c. .	8	1,590	2,600	1,010	—	—	Rickets.
288	+ coco-nut oil, 10 c.c. .	9	2,350	4,320	1,970	—	—	Slight rickets.

282, 283, 284, 285 were retrievers of the same family.

287, 288, were spaniels of the same family.

Both families were of the same age.

These experiments also were short, lasting 8–9 weeks. They were terminated by an outbreak of distemper which necessitated all the dogs being killed. In none of these cases was rickets very marked. Olive oil was the worst and lard also had slight rickets. Of the vegetable oils, coco-nut oil and pea-nut oil gave the best results. The suet dog was quite normal (Fig. 35).

The calcium oxide results show no striking difference throughout the whole series, the lard having the lowest percentage in the retriever set and the olive in the spaniel set. The experiments were too short to allow any significance to be attached to the calcium results, all of which were low because of the early termination of the experiments.

Radiographs of 282, 283, 284, and 285, taken 8–9 weeks after the beginning of the experiment, are shown (Figs. 34, 35, 36, and 37).

COMPARISON BETWEEN VARIOUS FATS.

General Diet.

Bread 100 grm.   Meat 10 grm.

Salt 1 grm.   Separated milk 175 c.c.

Orange juice 5 c.c.

Animals six weeks old at the start of the experiment.

No. of experiment.	General Diet.	Initial Weight.	Weight after 8 weeks 4 days.	Radiographic results after 8½ weeks.
		grm.	grm.	
303 (Fig. 40)	+ cod-liver oil .	1,060	2,600	Normal.
304 (,, 41)	+ rape-seed oil .	1,420	2,970	Slight rickets.
305 (,, 42)	+ cotton-seed oil .	1,070	1,950	Practically normal.
306 (,, 43)	+ olive oil . .	1,270	2,190	Rickets.
307 (,, 44)	+ lard . . .	1,290	2,810	,,
308 (,, 45)	+ bacon fat .	980	1,760	Almost normal (7 weeks).

In the radiographs taken after five weeks of diet the olive oil showed the worst rickets, lard the next worst, rape-seed oil slight rickets, the cotton-seed oil was practically normal, and the cod-liver oil was normal (Fig. 40–45). In this series olive oil and lard had the least anti-rachitic action. Except in the case of 303 (cod-liver) and 304 (rape-seed) the experiment ceased at an early age. The radiograph of 304 showed recovery from the slight rickets after twenty-two weeks of the experiment, but the shaft of the fresh femur contained only 9·8 per cent. of CaO, whereas there was 13·6 per cent. CaO in the

femur shaft of the cod-liver puppy killed at the same time. The difference in intensity of calcification of the periosteal bone in these two puppies is well seen in Figs. 128 (cod-liver) and 129 (rape-seed), which represents photographs of corresponding portions of bone shaft. It will be seen how much thicker the bone of 303 (cod-liver) is than that of 304 (rape-seed), and also how much further advanced is the laying down of bone in Haversian systems.

The Effect of Butter on Calcification.

The following experiments show the effect of adding small quantities of butter or meat protein, or both, to the standard diet. Four puppies were taken—290, 291, 292, 293.

General Diet.

Bread 100 grm.   Orange juice 5 c.c.
Separated milk 200 c.c.   Meat 10 to 20 grm.
Salt 1 grm.

Type—Cross between small retriever and Airedale.
Age at beginning of experiment, seven weeks three days.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh.	Histology results.
		weeks.	grm.	grm.	grm.	%	%	
290	+ 10 c.c. linseed oil	16½	2,920	6,270	3,350	18·4	10·5	Rickets.
291	+ 10 c.c. linseed oil and 10 grm. of meat protein.	16½	3,050	4,940	—	*24·3	9·8	Rickets. (not as bad as 290).
			Max. weight 6,500 grm. (ill)					
292	+ 5 c.c. linseed oil and 5 grm. of butter.	16½	2,760	5,590	2,830	24·3	13	Slight rickets.
293	+ 5 c.c. linseed oil, 5 grm. butter, and 10 grm. of meat protein.	16½	1,750	5,060	3,310	23·9	12·8	Practically normal.

* This high value is undoubtedly due to the absence of fat in the bone marrow as the result of inanition preceding death.

According to the radiographs, all these animals showed signs of rickets at some period of the experiment, 290 (no butter or meat protein) being the worst and 293 the most normal. The slightness of the rachitic condition at the epiphyses according to the radiographs was undoubtedly due to two factors :

 (1) The presence of meat in the diet even in the early stages of the experiment.
 (2) The animals were living out of doors from birth and throughout the whole period of the experiment.

The calcium and histological results show clearly that the addition of 5 grm. of butter per diem to the diets of 292 and 293 has had a beneficial effect on the calcification of the bones.

The addition of meat protein to the diets of 291 and 293 has had little or no effect on the calcification of the periosteal bone but has improved it at the epiphysis (see p. 40).

It may be added that these animals were most severely attacked by mange : in fact, because of the severity of the disease in 291, the experiment was concluded. It was interesting to observe how rapidly

292 and 293 (butter) recovered as compared with 290 and 291 (no butter). No doubt butter, although present in such small quantities, was responsible for the increased resistance to the skin infection.

COMPARISON BETWEEN SUET AND LARD.

In the following experiments the amount of bread eaten also came under close control.
Exps. 328 and 329.

General Diet.

Separated milk 175 c.c.   Salt 1 grm.
Bread 100–180 grm.   Meat 10 grm.
Orange juice 5 c.c.

Spaniel breed of puppy.
Age at beginning of experiment, seven weeks.
Confined to kennels throughout experiment.

No. of experiment.	Diet.	Duration. weeks.	Initial weight.	Max. weight.	Final weight.	CaO Fresh.	Dry.	Radiographic results.
328	G.D.+10 grm. suet	20	2,210	4,180 Nov. 1	4,180 Nov. 23	12·3	19·2	Normal.
329	G.D.+10 grm. lard	20	1,870	4,090 Nov. 1	3,490 Nov. 23	7·0	13·7	Very bad rickets.

The radiographs of these two puppies show in marked contrast the rachitic appearance of the bones of 329 (lard), Fig. 39, with the normal condition of 328 (suet), Fig. 38. 329 during the last three weeks was ill and lost weight. Before this illness, however, rickets had developed to a fairly severe degree.

COMPARISON BETWEEN BUTTER AND BUTTER WHICH HAS BEEN HEATED TO 120° C. FOR FOUR HOURS, OXYGEN BEING PASSED THROUGH IT WHILE HEATING.

General Diet.

Separated milk 175 c.c.   Salt 1 grm.
Bread 100 grm.   Lean meat 5 grm.
Orange juice 5 to 7·5 c.c.

Retrievers. No exercise. Energy of diet kept constant.
Age at beginning, 7½ weeks.

No. of experiment.	General Diet for 8 weeks.	Initial weight.	Weight after 7½ weeks.	Radiographic results after 8 weeks
321	+ 5 to 10 grm. oxidized butter.	2,090	3,850	Rickets.
325	+ 5 to 10 grm. normal butter.	1,800	3,120	Normal.

This experiment was made in consequence of the results obtained by Hopkins (15), who showed that butter heated in this way had lost its Fat-soluble A content. The butter was treated in the above described manner under Professor Hopkins's direction. The radiograph of 321 taken after eight weeks shows evidence of rickets, while

that of 325 is normal (Figs. 46 and 50). After being anaesthetized for this radiograph to be taken, the puppy (321) became ill and never ate its whole diet again. It was killed six weeks later, its weight having fallen from 3,850 grm. to 2,730. The fresh shaft of the femur was found to contain only 5·9 per cent. of CaO, one of the lowest figures obtained in this research. The heated and oxidized butter had apparently lost an element which influences the calcification of bone. Comparative radiographs of 321 (oxidized butter) and 325 (fresh butter) are seen in Figs. 46 and 50.

COMPARISON BETWEEN (1) COD-LIVER OIL, (2) COD-LIVER OIL HEATED TO 120° C. FOR FOUR HOURS, AIR BEING PASSED THROUGH IT DURING THIS TIME, (3) PEA-NUT OIL, (4) OLIVE OIL, (5) COCO-NUT OIL, (6) COTTON-SEED OIL.

General Diet.

Separated milk 175 c.c.   Lean meat 10–15 grm.
Bread 75–180 grm.   Salt 1 grm.
Orange juice 5 c.c.

Retrievers—7 weeks old at start of experiment. Confined to kennels throughout experiment.

No. of experiment.	General Diet.	Initial Weight.	Weight after 10 weeks.	Radiographic result after 10 weeks of diet.
336 (Fig. 52)	+ 10 c.c. cod-liver oil . .	2,430	5,020	Normal.
337 (,, 53)	+ 10 c.c. oxidized cod-liver oil	1,930	4,650	Normal.
338 (,, 54)	+ 10 c.c. pea-nut oil . .	2,310	4,920	Practically normal.
339 (,, 55)	+ 10 c.c. olive oil . . .	1,930	4,520	Fairly bad rickets.
340 (,, 56)	+ 10 c.c. coco-nut oil . .	1,620	4,520	Slight rickets.
341 (,, 57)	+ 10 c.c. cotton-seed oil .	1,800	4,420	Slight rickets.

Radiographic results which agree with the histological findings are shown in Figs. 52–57. The diet was well controlled during the experimental period of ten weeks, as can be seen in the growth curves of these puppies, Fig. 58. Except that the coco-nut oil puppy (340) put on rather more weight than the others, there is good parallelism in rate of growth among them all. The radiographic results are in close agreement with those obtained in experiments of the same type previously described. Olive oil is the worst of these vegetable oils and pea-nut is the best. In view of the destruction of the Fat-soluble A vitamine when butter is heated to 120° and oxidized at the same time, it is surprising that the radiograph of 337, in which case cod-liver oil treated in this way was eaten, shows no indication of rickets or defective calcification. Whether this difference between butter and cod-liver oil can be simply explained by the fact that cod-liver oil contains a much greater quantity of anti-rachitic vitamine than butter, so that the destructive change takes a longer time, or whether some other explanation must be sought, is not known. After ten weeks of the experimental feeding these puppies were anaesthetized for radiographic examination. 339 (olive) died under the anaesthetic, and 341 (cotton-seed), after recovery from the anaesthetic, became ill and gradually lost weight. After fourteen weeks of the diet the

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cod-liver and oxidized cod-liver dogs remained normal. Pea-nut oil (338) developed some rickets, but not to the extent of the coco-nut oil puppy (340). The order of potency as regards anti-rachitic effect from this series is again as follows : cod-liver and oxidized cod-liver oil, pea-nut, coco-nut and cotton-seed oils, and lastly olive oil.

SUMMARY.

Certain oils and fats have a great effect in promoting the calcification of bone and preventing the development of rickets, while others have no action in this respect. Of the fats tested, cod-liver oil is the best. Suet and butter also have a potent influence on calcification. Lard is poor as compared with suet. Butter, heated and oxidized for four hours, loses some anti-rachitic action. Cod-liver oil similarly treated still has a strong anti-rachitic effect. The vegetable oils vary in their anti-rachitic action, the order of merit being somewhat as follows : pea-nut and coco-nut oils (best), rape-seed, cotton-seed, palm-kernel, olive, linseed, and babassu oils (worst). Hydrogenated fats are poor.

(b) **The question as to whether the Anti-rachitic action of Fats can be explained by their Fat-soluble A vitamine content.**

I have now described experimental results which show that fats vary in their influence as regards the calcification of bone and the development of rickets. It is true that there is evidence that bone calcification (in any case periosteal bone calcification) and rickets as indicated by endochondral abnormality are not always identical problems; for in one experiment, the calcium content of the femur shaft was low (9·6 per cent.) (lard), Exp. 181, and there was no rickets, as judged by external appearance and the radiograph, while, in another puppy of the same family (butter), Exp. 182, there was evidence of rickets at the epiphyses when the calcium present in the femur shaft was higher (12·5 per cent.) (for radiographs see Figs. 12 and 13). In Exp. 182 winter butter was eaten, the puppy was confined, it ate much bread and became very fat. It gained 4,660 grms. in 19 weeks, whereas 181 (lard), which ate much less bread, only gained 2,890 grms. in 20 weeks. But otherwise the agreement in results was so general that I shall discuss the anti-rachitic action of fats and their power of promoting calcification as if they were synonymous ; for it is probable that the discrepancy mentioned above was due to some other factor of the diet—possibly bread—which in that series of experiments was not controlled.

To explain the variation in the anti-rachitic action of fats on other than a vitamine basis, such, for instance, as the saponification number, the degree of saturation of the constituent fatty acids or the presence of volatile fatty acids, seems hopeless. On the other hand, vitamines in general and, more especially as it concerns this work, Fat-soluble A in particular, are on as firmly established a basis as any other element in the diet, although, it is true, nothing is known of their chemical nature or mode of action. Were there any doubt as to the reality of the Fat-soluble vitamine, greater hesitation in the interpretation of the above-described results would be necessary.

Since there is no doubt on this point, and as there is strong but not complete evidence that the anti-rachitic action of certain fats is bound up with the Fat-soluble element, considered from the point of view of distribution and properties, it can only be assumed that the action of fats in rickets is due to a vitamine or accessory food factor which they contain, probably identical with the Fat-soluble vitamine.

The distribution and properties of the Fat-soluble vitamine have been worked out almost entirely by experiments on the growth of young rats, while, in these experiments showing the effect of fats on rickets, puppies only have been used. Now sufficient is known about variations in the mode of action of the same vitamine in different animals to prevent an investigator being surprised when some discrepancies are evident, and, before a new vitamine is added to the accepted list of three, it is essential that the balance of evidence for and against the identification of the new vitamine with one of the recognized three be carefully considered. This mode of procedure has been adopted in identifying the Water-soluble vitamine with the anti-beri-beri factor and, although some investigators still doubt whether they are the same, the balance of evidence is generally accepted as proving their unity.

Evidence has been obtained in this work which proves that neither the Water-soluble B nor the anti-scorbutic vitamine is responsible for the experimental results obtained in the fat experiments, and I shall proceed to discuss the question of the identity of the Fat-soluble A vitamine with the anti-rachitic substance in fats.

(1) The first point is their distribution. Both are most abundant in the animal fats except lard. Both are relatively deficient in or absent from the vegetable oils. The Fat-soluble vitamine is present in green vegetables but, unfortunately, no successful experiment has been carried through in this investigation proving the presence of the anti-rachitic vitamine in green leaves. The addition of green vegetables or their watery extracts to the diets of puppies gave rise to diarrhoea.

Dealing only with fats, it is clear that the general similarity of distribution of the anti-rachitic and Fat-soluble substances is striking but in detail differences are evident which call for qualification and amplification.

In 1918, when discussing this point in my first publication of this research, I stated that experiments on the distribution of the Fat-soluble vitamine had failed to recognize the presence of this substance in any vegetable oil. My results, however, pointed to the presence of the anti-rachitic vitamine in varying amounts in some of the vegetable oils and that vegetable oils were graded in their action in preventing rickets and promoting calcification of bones. The best of these included pea-nut and coco-nut oils. Linseed, babassu, and hydrogenated fats were the worst oils, while in an intermediate position were found cotton-seed, rape-seed, and palm-kernel oils. At this time I stated that either the Fat-soluble and the anti-rachitic vitamines were different or that the puppy experiments were a more sensitive test as to the presence or absence of the vitamine than the experiments on the growth of rats.

During the past months a part of this difficulty has been removed by the recognition that some of the vegetable oils and lard contain Fat-soluble A. For instance, Daniels and Loughlin (16) have shown that lard and cotton-seed oils are both capable of providing sufficient Fat-soluble vitamine when added to purified synthetic diets devoid of this substance to allow in rats growth, reproduction, and rearing of young. It is true that these fats had to be added in larger quantities (28 per cent. and 21 per cent.) than is usual in such experiments, so that the fact that they contain less of the vitamine than cod-liver oil, suet, and butter is certain, but there seems no longer any doubt that they contain some of the Fat-soluble accessory food factor. Lard contained more than cotton-seed oil. The results are in accordance with my rickets experiences, for lard was on the whole more potently anti-rachitic than cotton-seed oil but not so good as the other animal fats, while cotton-seed oil was better than linseed and olive oils.

Recently also Prof. Hopkins informed me that he had obtained evidence of growth factor in rape-seed oil which is a fat having some of the anti-rachitic vitamine as tested by its action on the production of rickets in puppies. No doubt in the immediate future it will be proved that other vegetable oils contain the Fat-soluble vitamine. I suggest that pea-nut and coco-nut oils are worth investigating from this point of view. It is evident that a part of the discordant facts as to the graded anti-rachitic action of oils and the earlier teaching that lard and the vegetable oils were devoid of the Fat-soluble vitamine is disappearing rapidly since the first publication of my experiments. Obviously much work remains to be done along these lines before complete concordance of results will be obtained.

(2) It has been pointed out above that after a certain age, about four months, it is very difficult to produce rickets in normal puppies by vitamine deficiency in the diet ; that is to say, puppies become more independent of the anti-rachitic vitamine from the point of view of bone calcification, especially bone having its origin in cartilage. So also young rats, after obtaining a certain growth, do not stop growing when the Fat-soluble vitamine is excluded from their diet. Rats, in fact, develop a mechanism which makes them less susceptible, from the point of view of growth, to deficiency of this vitamine in the diet. This similarity in behaviour of dogs and rats, in that both develop with increasing age greater independence to vitamine activity as regards such dissimilar functions as calcification of bone and growth, is evidence in favour of the identity of the anti-rachitic and the Fat-soluble vitamines. The question is complicated, for puppies do not develop rickets unless they grow and the more rapidly they put on weight at the expense of substances like bread (see p. 42), the more severe will be the rickets. In the case of young rats, however high the energy of the food eaten, they will not continue to grow unless there is a supply of the Fat-soluble vitamine. Puppies, on the other hand, grow well when there is only a minimum of Fat-soluble A present in the food. It is unlikely that the food of the puppies which developed rickets was entirely devoid of this vitamine, but it can be safely stated that it was only present in very small amounts, and

that the growth of the puppy had no relation to the amount eaten. If, at the end of this period, bad rickets had developed, then the animal often went off its food and its weight declined. Generally a puppy receiving linseed oil would grow during the early months as well as one getting cod-liver oil if they ate equivalent amounts of other foodstuffs. The weight curves seen in Fig. 58, where the diets were closely controlled and everything was constant except the type of fat eaten, are good evidence of the independence of growth and the amount of Fat-soluble A eaten, for it will be seen how parallel are the rates of growth of these puppies. Since 175 c.c. of separated milk was one of the elements in the diet, it is certain that some Fat-soluble vitamine was eaten, but, in the case of animals of 4,000 grm. weight, this amount must have been exceedingly small. It would be interesting to carry out experiments in which puppies were fed on synthetic diets of the purified elements similar to those used in the rat feeding work. If puppies could be got to eat a diet of this nature, it would settle the question as to whether the Fat-soluble vitamine is as essential for growth in the case of puppies as it is in rats. I am doubtful whether, in applying vitamine results to children, too much is not being made of their effect on growth. This opinion depends not only on the results of feeding puppies on vitamine-deficient diets but also on the observations on children made by Hess and Unger (17). These workers fed children on separated milk powder, sucrose, autolysed yeast, cereal and cotton-seed oil, under the impression that all these substances were devoid of Fat-soluble A. Even over a period of fifteen months' feeding on this diet, the children grew, although at a less rate than normal. Hess and Unger decided that Fat-soluble A cannot be a factor of practical importance in the growth of children because it is unlikely that the diet of a child would ever contain as small a quantity of this vitamine as in the above-described diet. With their further conclusion that Fat-soluble A or a vitamine with a similar distribution which I have called the anti-rachitic vitamine, has but little to do with rickets in children, I do not agree. I have referred to this work in an earlier publication (2), and will discuss it again in a later paper.

The question arises as to whether any suggestion or explanation of the different susceptibility of the young rat and puppy as regards growth to the Fat-soluble factor of the diet can be made. It may be a question of age and length of time of reaction. Probably the puppy develops some mechanism making it more independent of the anti-rachitic factor before it is 5–8 weeks old. Certain it is that the younger the puppy the greater is the difficulty in getting growth and retaining health on these diets deficient in Fat-soluble vitamine.

It is evident that the question of the relative importance of Fat-soluble A in the growth of rats as compared with the growth of puppies and children cannot be settled without further experiment, but there is good evidence that it does not hold the important position in the latter animals that is generally assumed by those engaged in the rat-feeding experiments.

Besides the similarity in reaction between the growth of rats

and the production of rickets in puppies, in which cases there develops in the animals a greater independence to the Fat-soluble and anti-rachitic vitamine respectively, there is one other physiological point of agreement in reaction which appears suggestive. When young healthy rats are suddenly placed on a synthetic diet devoid of Fat-soluble A, the effect of the deficiency is not noticed at once. The rats usually continue to grow at a normal rate for about twenty days. The effect is by no means immediate. Similarly in the case of feeding on diets deficient in anti-rachitic vitamine, the effect is slow and even under the best rickets-producing conditions there is usually but little result under six weeks of treatment. The calcium metabolism and balance seem to be very little influenced, as evidenced by the calcium content of the bones, until the puppy has eaten the diet deficient in anti-rachitic factor for some weeks. When, however, we consider either rats or puppies whose diets have been deficient in Fat-soluble vitamine so that, in the one case, growth has ceased or, in the other, rickets has developed, then the addition of a fat containing the vitamine immediately produces its effect by stimulating growth and by improving the calcification of bone in the respective cases.

These facts of agreement from the point of view of physiological reaction seem to me strong evidence that the substance in fats stimulating the calcification of bone is the same as Fat-soluble A, i. e. the factor which stimulates growth in rats. Their delayed action in the healthy animal also suggests that both effects, stimulation of growth and calcification of bone, are indirect and not direct. The greater independence of older animals indicates the same type of action.

(3) The third point as to the identity of the Fat-soluble and anti-rachitic vitamines involves a consideration of the properties of these bodies, apart from their distribution and mode of action. It is necessary to add that, even in the case of the Fat-soluble vitamine, we know very little and our knowledge as to the properties of the anti-rachitic vitamine is much more scanty.

Effect of Heat. There is some discordance of results as to the susceptibility of Fat-soluble A to heat but the work of Osborne and Mendel (18), who showed that butter treated with steam for $2\frac{1}{2}$ hours still retained its growth-promoting qualities, is generally accepted as correct. In other words, Fat-soluble A is strongly resistant to heat when present in fats. In the case of cod-liver oil there is strong heat resistance so far as the anti-rachitic action is concerned. Experiments are quoted above (229, 231, and 232) (p. 24) where cod-liver oil was heated to 120° C. for periods of 2 and 4 hours. There was no evidence of destruction of the anti-rachitic vitamine after two hours' heating, but in the case of four hours' heating there may have been some slight destruction as, at one period of the experiment, the radiograph of this animal was not quite normal. The abnormality, however, was very small and may have been due to an uncontrolled factor, viz. the amount of bread eaten. It was quite clear from this experiment that the anti-rachitic vitamine like the Fat-soluble vitamine is strongly thermo-stable.

The effect of oxidation and heat. Part of the discrepancy in the

experimental results as to the effect of heat on Fat-soluble A is no doubt due, as pointed out by Hopkins (15), to the possibility of oxidative changes being allowed to proceed side by side with the heating process. For he has shown that, if oxygen is allowed to pass through heated butter, the Fat-soluble vitamine is readily destroyed. Rickets experiments were carried out to see if there was much anti-rachitic vitamine left in butter heated to 120° for four hours with oxygen passing through it continuously. This process was kindly carried out in Prof. Hopkins's laboratory. It was found that animals fed with this fat had extremely little calcium in their bones as compared with animals similarly fed but eating the untreated butter. There was no doubt but that the anti-rachitic vitamine had been to some extent destroyed when butter was treated in this way (see Exp. 321-5) (see p. 29).

In order to emphasize more strongly the difference between a normal oil and the same after subjection to heat and oxygen, I tried the effect of cod-liver oil which had been heated to 120° C. for four hours while oxygen was passed through it. Both the animals, the one receiving the untreated oil and the one receiving the oxidized oil, remained normal (Exp. 336 and 337), and there was no evidence of the destruction of the anti-rachitic vitamine. If it should happen that four hours' heating and oxidation at 120° C. also leaves a large amount of Fat-soluble A in the cod-liver oil, it will go a long way, especially when considered together with the butter results, to clinch completely the identity of Fat-soluble A and the anti-rachitic vitamine.

I have now discussed the question whether the anti-rachitic action of certain fats is due to their Fat-soluble A content. It is clear that there is strong evidence in support of the contention that the promotion of growth of young rats and the increased calcification of bones of puppies are due to the same vitamine in fats. Some points still await investigation and, until this work has been done, it cannot be confidently asserted that they are identical substances. It is important that further attempts should be made by experiments on the growth of rats to see if more data as to the distribution of Fat-soluble A in vegetable oils can be obtained in accordance with the anti-rachitic action of fats as explained above. Another problem urgently requiring solution is an investigation into the anti-rachitic action of green vegetables.

The interaction of the anti-rachitic vitamine with the other elements of the diet and environment, some of which work hand in hand with the vitamine, while others antagonize it and have a rickets-producing effect, will be dealt with in other sections of this publication.

Summary.

(1) The evidence is discussed as to whether the action of fats in the development of rickets is due to a vitamine, and whether this vitamine is the same as Fat-soluble A. The distribution of the substance in fats having the anti-rachitic action and the few properties as regards heat and oxidation which have been investigated, lend strong support to its identification with Fat-soluble A.

(2) The time relations of the reactions in growth and rickets

experiments produced by the various fats are similar. In both cases, when vitamine-deficient but otherwise adequate diets are given to well-fed healthy rats and puppies, there is a long interval before their effect on growth and calcification respectively is obvious. When the animals are suffering from the deficiency the addition of a good fat to the diet produces its effect quickly.

Rats as regards growth and puppies as regards rickets become more independent of the vitamine as they grow older. These facts are in favour of Fat-soluble A being also responsible for the anti-rachitic action of certain fats.

(c) The Influence of Meat and its Constituents.

Meat has long had the reputation in therapeutics of assisting in the curative treatment of rickets in children. So far as I know, the knowledge was purely empirical, and it was one of the recommendations among others, such as the addition of milk and cod-liver oil to the diet, made in the treatment of rickets. The fact that fresh scraped meat is given in this disease suggests that, when introduced as a therapeutic agent, infantile scurvy may have been either the disease treated or a complication of the pathological condition.

In the case of puppies, the addition of meat to diets devoid of this substance reacts favourably on their health. It is the first substance to be picked out of a food mixture, and it is evident that its special position of favour is justified by the important part it plays in nutrition. The addition of 10 grm. of meat a day to the standard diet will often transform a puppy, off its food and losing weight, into a vigorous animal, eating its full ration and putting on weight. So striking is this effect that, in most of the later experiments where it has been necessary to make each puppy of a series eat its diet quantitatively, meat has formed an element of the food. It might be expected that meat would have an anti-rachitic action. That this is the case I shall now show. After demonstrating its action in inhibiting the development of rickets, I shall discuss the limitation of its anti-rachitic effect. In all the experiments described below the fresh meat given had the fat dissected off as far as was possible.

COMPARATIVE EFFECT OF ADDING 10 AND 50 GRM. OF MEAT TO A RICKETS-PRODUCING DIET.

General Diet :

Separated milk 175–250 c.c. Orange juice 3 c.c.
White bread. Linseed oil 10 c.c.
Yeast 5 grm. Salt 1 grm.

Age at beginning 7 weeks.

No. of experiment.	General Diet.	Duration. weeks.	Initial weight. grm.	Final weight. grm.	Gain. grm.	CaO in femur. Fresh. %	Histology results.
174	+ 10 grm. lean meat.	22	1,800	5,115	3,315	8·7	Rickets.
175	+ 50 grm. meat .	22	2,040	6,625	4,585	9·04	Rickets (less than 174).
172	+ 10 grm. butter, + 10 grm. meat.	22	1,600	5,575	3,975	13	Nearly normal.

Radiographs of 174 and 175 taken after thirteen weeks of the experiment are shown in Figs. 60 and 61. Whereas both animals developed rickets, 174 receiving only 10 grm. of meat per diem was slightly worse, although it grew at the slower rate. It will be noted that the bones in both animals had a low calcium content, but the radiographs and histological sections show that rather more severe rickets was present in 174. This is one of the characteristic effects of meat. Its action on endochondral calcification is more easily observed than on the calcium deposition in periosteal bone. In some cases the radiographic appearance obtained in animals eating meat together with a rickets-producing diet may appear more normal than the histological picture and calcium content of bone would lead to expect. There was no puppy in this series not eating some meat, so that these results cannot be contrasted with a control of the same litter. Reference, however, to other puppies of the research on the same diet as above, not eating meat, will show that the rickets of 174 (10 grm. of meat) was not so strongly developed as it would otherwise have been—compare Fig. 60 with Figs. 7 and 95. Fig. 59 is a radiograph of a puppy of the same series as 174 and 175 which received an additional 10 grm. of butter. This has protected the animal against rickets better than the extra 40 grm. of meat eaten by 175.

COMPARATIVE EFFECT OF DIETS WITH AND WITHOUT MEAT.

General Diet :

Separated milk 175 c.c. Orange juice 5 c.c.
White bread 50–180 grm. Linseed oil 10 c.c.

Puppies probably not of same family but of same age.

No. of experiment.	General Diet.	Other Conditions.	Duration. weeks.	Initial Weight. grm.	Weight after 8 weeks. grm.	Gain. grm.	Radiographic results.	Histology results.
351	+ 20–30 grm. lean meat	Liberty during day.	16	1,380	2,660	1 280	Very slight rickets.	Some rickets.
352	—	Liberty during day	16	1,370	2,960	1,590	Rickets.	Rickets.
353	+ 20–30 grm. lean meat	Confined to kennel	16	1,730	3,930	2,200	Slight rickets.	Rickets.
354	—	Confined to kennel.	16	1,760	3,730	1,970	Rickets.	Bad rickets.

In this experiment all articles of diet were eaten quantitatively. The kennels were in the open air throughout the experiment. From the point of view of the effect of meat, 351 and 352 are comparable, similarly 353 and 354. The radiographs of these puppies taken 8 weeks after beginning experiment are seen in Figs. 62–65. Very slight rickets is present in either of the animals eating meat, 351 and 353, but 352 and 354 (no meat) have both developed fairly advanced rickets. The contrast in the epiphyseal swellings at the wrist-joints was interesting, both the meat-eating animals remaining more nearly normal while 352 and 354 (no meat) developed the characteristic swellings. This series of experiments will be referred to again in the

section dealing with exercise. Growth curves of these puppies are shown in Fig. 66.

Although it is evident from the above experiment that the anti-rachitic effect of meat is a real thing, more particularly as regards the epiphyses of bones, very bad rickets can be produced in large rapidly growing dogs, eating a lot of bread, even when as much as 50 grm. of fresh lean meat are added to the diet. The following experiments illustrate this point.

General Diet:

Separated milk 175 c.c.   Bread *ad lib.*
Yeast 5–10 grm.   Linseed oil 10 c.c.

Retrievers.   Age at beginning 7 to 8 weeks.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft Fresh.	Dry.	Remarks.
		weeks.	grm.	grm.	grm.	%	%	
141	+ 5 grm. meat.	20	2,490	5,820	2,330	7·19	17·48	Rickets
143	+ 20 grm. meat	20	2,890	4,400	1,510	9·48	17·88	Rickets. Ill towards end of experiment.
144	+ 50 grm. meat	20	3,690	8,825	5,735	10·72	15·74	Very bad rickets.

Rickets developed in all these puppies, 144 being very bad in spite of receiving most meat. Fig. 51 is a radiograph taken some time after death, and is therefore rather blurred, but still conveys the impression of the intensity of the disease. This animal gained weight very rapidly, owing to the large amount of bread eaten in addition to the meat. Since increasing the bread in a diet, other things being equal, increases the rickets produced (see section on bread), and since the addition of meat creates the desire to eat more bread, it is clear that the anti-rachitic effect of meat may be more than counterbalanced, especially in a large breed of dog, by the increased amount of bread eaten. This has happened in Exp. 144 (Fig. 51). It is of interest to note that, although 144 had apparently the worst rickets in this series, its periosteal bone contained the highest percentage of calcium.

The question now arises to what the anti-rachitic action of meat is due. It may be stated at once that this problem has not been solved. The action seems to be of an altogether different order from that of the fats containing the anti-rachitic vitamine. It may be suggested that it is due to the small amount of vitamine associated with fat which cannot be removed from the meat by dissection. This is a possible, but, in my opinion, an unlikely explanation of its whole action. In an earlier publication I suggested that its beneficial effect was possibly due to its stimulant action on the metabolism (specific dynamic action), which in the case of meat is high. It can readily be imagined that anything which stimulates metabolism will bring into greater action any anti-rachitic vitamine either in the food or in the animal's body. And on this basis the effect of meat as an adjuvant to the anti-rachitic action of other physiological substances might be placed. This explanation would put the anti-rachitic action of meat and that of exercise on a similar basis, and I think there

is something in common between the two since both appear to be of a secondary nature to the anti-rachitic vitamine. If, however, the stimulation to metabolism alone were the real explanation of the action of meat in rickets, it would be expected that any method of increasing metabolism would produce an anti-rachitic effect. For instance, thyroid extract might be expected to assist in preventing rickets. Recent experiments performed to decide this point have not led to the expected result, for in spite of large daily doses of thyroid gland, rickets developed almost as severely as in the control animal receiving no thyroid. In the experiments quoted below (p. 69) there was no doubt that the thyroid in the diet stimulated the metabolism, because, although both animals ate food containing the same constituents and same amount of energy, the puppy receiving thyroid put on weight much less rapidly. In view of this result with thyroid, I am doubtful whether the anti-rachitic effect of lean meat can be satisfactorily explained by its specific dynamic action and the increased metabolism it produces. The action of meat in preventing rickets is also probably closely related to its effect in improving the health and general disposition of young animals, a fact previously alluded to, and the solution of the latter problem would also no doubt explain its anti-rachitic effect.

Finally, there is always the possibility that the anti-rachitic effect of meat, under some conditions, may be due to its power of promoting the digestion and absorption of other foodstuffs from the alimentary canal.

A few experiments have been made to see whether the action of meat in inhibiting rickets is due to its protein or to its extractive content. The problem is especially difficult because the anti-rachitic action of meat *per se* is small, and it is therefore necessary to control closely all the other elements of the diet in addition to the environment.

In the following experiments (299 and 301), in which everything was closely controlled, it will be seen that meat protein has some anti-rachitic action, more particularly obvious at the points of endochondral ossification, but once again, as in the case of meat, with no effect on the calcification of the periosteal bone.

Exp. 299 and 301 :

General Diet :

Separated milk 200 c.c.	Salt 2 grm.
Bread 70–175 grm.	Linseed oil 10 c.c.
Orange juice 5 c.c.	Meat 10–20 grm.

Age at beginning about 6 weeks.

No. of experiment.	General Diet.	Duration.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Fresh bone.	Dry bone.	Radiographic result.	Histology result.
		weeks.	grm.	grm.	grm.	%	%		
299	+ 20 grm. meat protein	18½	2,340	6,650	4,310	9	12·8	Almost normal.	Rickets.
301	+ 30 grm. bread	18½	1,800	6,560	4,760	9·25	13·3	Rickets.	Bad rickets.

The energy of the diets of these dogs was kept as constant as possible, that is to say, the meat protein of 299 replaced bread; 30 grm. of bread being regarded as equivalent to 20 grm. of meat protein. Both animals at the end of the experimental period looked rachitic. The radiographs show 301, Figs. 69 and 72 (no meat protein) to have developed the condition to a more severe degree than 299, Figs. 67 and 70. Histological evidence of the bones shows 299 to have obvious rickets but not as bad as 301. It is clear then that the substitution of bread by meat protein has slightly reduced the rickets at the epiphyseal ends. It will be further seen, however, that the long bones of 299 are by no means normal, and, in fact, contain slightly less calcium than those of 301, which radiographically and histologically has worse rickets. Both calcium results are below the normal. For other experiments on meat proteins see Exps. 290, 291, 292, and 293, p. 28. Thus we see that the action of meat protein is very similar to that of lean meat itself. In Exp. 299, 20 grm. of meat protein were added to the diet. This is equivalent to 100 grm. of meat, a large ration for a puppy in this research, and, as compared with the amount used in the meat experiments, a quantity which might be expected to produce a greater anti-rachitic effect than that observed. It seemed probable, in fact, that the extractives of meat were responsible for some of the inhibitory action on rickets development possessed by meat.

Several series of experiments have been made to test the action of meat extract in rickets. The earlier results pointed to a definite anti-rachitic effect, but later work, when other factors were more closely controlled, suggested that this action was smaller than previously indicated. Before making a definite pronouncement on the extent of the anti-rachitic effect of meat extracts, I wish to repeat the earlier work under more precise conditions. In the meantime it is safe to say that the effect of meat extractives is less than that of meat itself.

The effect of meat on the development of rickets will be considered later in relation to exercise and confinement.

Summary.

(1) Lean meat has a definite anti-rachitic effect. Its action in this respect is, however, of a secondary nature and is probably more prominent in assisting any anti-rachitic vitamine there may be present in the diet. When freedom is allowed to the puppy, meat increases its activity (see p. 64).

(2) Its anti-rachitic action may to a slight degree be due to anti-rachitic vitamine contained in the fat inseparable from it by dissection, but this does not explain the whole effect. The health of the animal is greatly benefited by the addition of small quantities of meat to the diet, and the basis of this improvement in health, whatever it may be, probably also affords the explanation of its inhibitory effect on rickets development.

(3) It appears to assist calcification processes at the epiphyses more prominently than the calcification of periosteal bone, so that the

radiographs may appear nearly normal when the calcium content of the bone shafts is subnormal.

(4) The protein of meat has the same kind of inhibitory action as meat itself, but to a less degree. A definite pronouncement as regards the anti-rachitic action of meat extractives which, in any case, is small, must wait until further experiments are completed under more precise conditions.

(d) The Influence of Bread and Carbohydrates.

Many clinicians, Cheadle (19), have thought that excessive carbohydrate plays a part in the production of rickets, and I now propose to give experimental proof that this is the case.

Although bread has formed an element of the diets employed to produce rickets in puppies since the early days of this work, it was a long time before it was clearly established that, not only had bread no anti-rachitic action, but that it was a most important substance in actually making the condition worse. All investigations are influenced by the results obtained in allied experimental work, and there was practically no indication from the beri-beri and scurvy researches that the presence of any element in the diet could be considered as having a disease-producing effect. These deficiency diseases were (and are) usually held to be the result pure and simple of deficiency respectively in the anti-beri-beri and anti-scorbutic factor. The results to be described will make it clear that rickets cannot be classed as a ' deficiency disease ' in this sense of the word.

In my first publication on rickets I emphasized the close relation between rickets and growth. Not only is growth essential before rickets develops but also the greater the growth (in this case the greater the increase in weight [1]) the worse is the condition of rickets produced. Only slowly did the idea crystallize that excess of [2] bread might be responsible for the exaggeration of the rachitic syndrome.

The earliest experiments, where the action of bread became apparent, have already been described (p. 24). Three puppies (220, 221, and 223, Figs. 15, 21, 18) were on similar diets containing palm-kernel oil, and all the elements of the diets were carefully measured except the bread, which was given according to the dogs' appetites. 220, which ate most bread and put on weight very rapidly, developed very bad rickets, while in the same period 221 had only slight rickets. Intermediate from the point of view of rickets was 223, which put on weight at a pace intermediate between 220 and 221. Unfortunately in this series of experiments no tally was made of the actual amount of bread eaten. In repeating the experiment on other puppies, a record of the amount of bread eaten was obtained. All the other elements of the diet, except bread, remained constant.

Puppies 319 and 320 ate

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[1] For the purpose of this paper I am using these words as synonymous and this use is not strictly accurate.

[2] It will be clear from the work described in this paper that ' excess ' and ' deficiency ' of a dietetic element can only be considered as such after reference to the other elements of the diet.

General Diet.

Separated milk 200 c.c.	Salt 1 grm.
Orange juice 5 c.c.	Meat (10 grm. first 4 weeks).
Linseed oil 10 c.c.	

In addition there was given

| 319 | 320 |
| 100–250 grm. bread. | 75 grm. bread. |

Type of puppies, Black Lurchers.
Age at beginning, eight weeks.
Animals confined to kennels throughout.

In eight weeks 319 (large amount of bread) increased in weight 1,560 grm. In the same period 320 (small amount of bread) increased in weight 840 grm. In this period 319 (Fig. 74) had developed advanced rickets, whereas 320 (Fig. 73) was much more normal.

As often happened in these experiments, after severe rickets had developed, 319 refused to eat its diet completely, and its weight declined from 5,100 grm. to 4,850 in the last fifty-three days of its life. In this same period 320 (less bread) increased in weight from 3,330 to 3,650 grm. (Fig. 75). At death the following percentages of CaO were found in the shafts of the femurs of these dogs.

No. of experiment.	Percentage of CaO in fresh femur.	dry femur.	Histology results.
319 (Fig. 74) . . .	9·1	18·3	Bad rickets.
320 (Fig. 73) . . .	11·2	18·5	Rickets.

The calcium content of the fresh bones, which, as previously explained (p. 10), is the important number, shows that 319 had developed worse rickets as the result of eating a greater quantity of bread. The minute anatomy of the bones agreed with the radiographic and chemical results. See Figs. 118 and 119.

In the following series also the amount of bread eaten was the only variable in the diet.

Puppies 333, 334, and 335 ate

General Diet.

Separated milk 175 c.c.	Orange juice 5 c.c.
Meat 5–20 grm.	Salt 1 grm.
Linseed oil 10 c.c.	

Type of puppies—terriers.
Age at beginning, eight weeks.
Confined (indoors) to kennels throughout.

They received in addition

| 333 | 334 | 335 |
| 50 grm. bread. | 100 grm. bread | 150–180 grm. bread. |

The weight curves of these puppies is shown in Fig. 79. It will be seen that in a period of ten weeks :

333 increased from 1,500 to 2,470— 970 grm. gain.
334 „ „ 1,600 to 3,330—1,730 „ „
335 „ „ 2,100 to 5,090—2,990 „ „

The radiographs show that 335 (Fig. 78) has very bad rickets, 333 (Fig. 76) slight rickets, while 334 (Fig. 77) is intermediate between these two.

Percentage CaO in femur.

No. of experiment.		Fresh shaft.	Dry shaft.	Histology
333 (Fig. 76) .	.	10·95	17·5	Rickets (Fig. 126).
334 (Fig. 77) .	.	8·92	14·7	Rickets.
335 (Fig. 78) . .	.	8·32	13·9	Bad rickets (Fig. 127).

The calcium content of the shafts of the bones are in keeping with the radiographic results, the animal with the worst endochondral calcification having also the smallest percentage of CaO in the periosteal bone.

In this experiment also the dog that developed the worst rickets as the result of eating most bread became ill during the latter weeks and declined in weight from 5,090 to 4,510 grm. in the course of the last three or four weeks. Neither 333 nor 334, eating smaller quantities of bread, suffered in this way, but they continued to eat their full ration and gained weight slowly.

In view of the above results no doubt can remain but that, when eating diets capable of producing rickets, the severity of the disease depends upon the amount of bread eaten, the larger the amount consumed the more severe is the disease produced, when all other factors are kept constant.

Although experiments have not been made to determine the point directly, it is probable that other cereals would act in a similar way to bread, for in earlier experiments it has been shown that oatmeal and polished rice in the diet of puppies are compatible with the development of rickets. I think it probable, however, that differences will be shown among the cereals. I should expect that oatmeal would not be so rickets-producing as white wheaten flour, nor unpolished as bad as polished rice. It may be added that oatmeal contains five times as much CaO as white wheaten flour and natural rice thirteen times as much as polished rice.

In view of the above results I attempted to find out whether any particular constituent of the bread was more important than others in producing rickets. In this quest some success was obtained, for there is evidence that pure carbohydrate is capable of producing bones that are more defectively calcified. Several attempts were made to test this point, but the great difficulty met with was that the puppies became ill when given diets deficient in the anti-rachitic vitamine and containing, at the same time, excess of pure carbohydrate. To establish a fact of this nature it is essential that the puppies should eat the diets quantitatively. Resort had finally to be made to the replacement of linseed oil, which is one of those oils containing the least anti-rachitic action, by lard, which is rather more antagonistic to rickets and is compatible with better health under the conditions of the experiments. The meat ration was also increased to 20 grm.

In the following series of experiments severe rickets was not produced in any case, and the best indication of the detrimental action

of the additional carbohydrate (glucose) can be seen in the calcium results.

Experiments 295, 296, and 297 received as a

General Diet.

Separated milk 200 c.c.   Orange juice 5 c.c.
Bread 100 grm.   Lard 10 grm.
Meat 20 grm.

Eight weeks old at beginning.

No. of experiment.	Diet	Duration. weeks.	Initial weight. grm.	Final weight. grm.	CaO in femur shaft Fresh. %	Dry. %
295	+ 50–90 grm. of glucose per diem	19	2,410	6,330	9·6	12·7
296	+ 10–30 grm. of glucose per diem	19	1,870	4,080	11·6	15·9
297	General Diet only .	19	1,810	4,460	14·0	18·8

The radiographs show that 295 (most glucose) was most rachitic but, even in this case, the degree of rickets as indicated by defective endochondral calcification was not great. 297 (no glucose) was almost normal. The chemical results also show that the more carbohydrate eaten the greater the defect in bone calcification, when all other factors of diet and environment are constant. The histological results are in accord with the chemical determinations.

It is probable, then, that the carbohydrate moiety of bread is largely responsible for the fact that increasing the intake of this substance relatively to the rest of the diet makes the severity of the disease worse. Bread may contain other offending constituents, but this problem has not been worked out.

How the action of bread in producing rickets is to be explained can only be a matter of conjecture at this stage. Like meat it is deficient in both Fat-soluble A and calcium salts, but as regards rickets its action is opposite in nature to that of meat. Whereas meat tends to diminish or prevent the increase of epiphyseal swellings, bread encourages their hypertrophy. Meat increases endochondral ossification, bread inhibits it. It is true that the greater the amount of bread eaten the greater is the increase in weight and formation of new tissues, and this in itself must result in a more urgent call on the calcium in the body, so that less is available for the calcification of bone. But the same effects are produced by eating more meat, which does not have the rickets-producing action. However, the comparison cannot be pressed because in the bread-variable experiments, bread amounting to 100–250 grm. was eaten each day, whereas in the meat-variable experiments the meat did not exceed 50 grm. per diem. With amounts of meat, comparable to those used in the bread experiments, it might be found that this foodstuff also increased the severity of rickets. Certainly very bad defects in calcification of bone can be produced when rapidly growing puppies eat fair quantities of meat (see Exp. 144) if the diets are otherwise unbalanced and especially when excess of bread is eaten.

The detrimental action of excessive bread on the health of the puppies is a most striking fact. It must be remembered that the

diets in these cases were also deficient in Fat-soluble A and the animals were not being exercised. But the bad results of feeding were certainly due to the bread, for when this was reduced or kept low these animals remained comparatively healthy. The large amount of bread produced, in the first place, slowness of movement, then lethargy, and in some cases, paresis, especially of the hind legs. Ultimately the puppies refused to eat up their food, lost weight, and looked generally miserable.

Summary.

(1) Increasing the bread in diets deficient in the anti-rachitic vitamine, has a great influence in increasing the severity and rate of development of rickets, especially in animals receiving no exercise. This statement probably holds also for other cereals, but the point has not been proved.

(2) In one series of experiments it was shown that glucose also produced more defective calcification of bone, so that it is possible that the carbohydrate moiety of bread is largely responsible for this detrimental action.

(3) Under the conditions of the above described experiments, excessive bread, besides its inhibitory action on calcification, had a very bad effect after six to ten weeks on the general health of the animals, which ultimately became lethargic, refused food, and lost weight. In view of the large part bread plays in the dietary of the people, the above facts cannot be too strongly emphasized.

(e) The balanced action of Milk constituents.

In earlier sections of this publication it has been seen that dietetic elements have two actions, the one stimulating calcification processes and preventing rickets, the other inhibiting these processes and tending to produce rickets. The result depends on the nature of the balance of these actions. This generalization is crude because it expresses neither the close interplay between all the dietetic elements among themselves nor the dependence of their actions on the environment nor the fact that rickets is something more than defective calcification. In this chapter I wish to describe some preliminary experiments made to elucidate the action of milk constituents in rickets and to show the importance of the balanced effect produced by these elements as they are normally found in this food. It will be seen that, when the constituents of milk are altered in relation to each other, detrimental developments may occur in the animal ingesting them.

(i) ' Casein '.

Meat has been shown to have a definite action in aiding calcification of the endochondral bone, although but slight effect on that of the periosteal bone, and the same type of action, but to a smaller degree, was produced by meat protein. It might be surmised therefore that casein would act similarly. In the earlier experiments performed, it was found that, contrary to expectations, casein had but little action on the development of rickets. In later experiments, however, the casein preparation used hastened the onset of rickets—

or a condition almost identical with it so far as the external appearance of the animal and radiographic examination are concerned—to an advanced degree. Closer investigation of the problem made it apparent that the effect obtained depended on the type of casein employed. In the earlier experiments ' edible casein ' was added to the diets. This preparation was alkaline and went into solution more readily. The substance used later was caseinogen. It was acidic in reaction and no doubt prepared from milk by acid precipitation. Both preparations were commercial. I shall describe the results obtained with these substances separately.

Edible Casein (alkaline in reaction).

Exp. 300 and 301.

General Diet.

Separated milk 200 c.c.   Orange juice 5 c.c.
Bread 70–175 grm.   Meat 10–20 grm.
Linseed oil 10 c.c.   Salt 2 grm.

Retrievers.
Age at beginning about 6 weeks.
Confined to kennel throughout.

No. of experiment.	Diet.	Duration. weeks.	Initial weight. grm.	Final weight. grm.	Max. weight. grm.	CaO in Fresh bone. %	CaO in Dry bone. %	Histology results.
300	+ 20 grm. casein	18½	2,150	5,010	5,420 (after 15 weeks.)	7·7	18·4 (no fat in marrow in bone).	Rickets.
301	+ 30 grm. bread	18½	1,800	6,560	6,560	9·25	13·3	Bad rickets.

Energy of food eaten was practically constant for first 15 weeks.
After 15 weeks of the experiment, 300 (casein) went off its food and its weight decreased from 5,420 to 5,010 grms. The relatively high calcium content in percentage of the dry bone in 300 is due to the absence of fat in the bone marrow which disappears early in illness. When the experiment had continued 13 weeks, the radiographs (Figs. 68 and 69) of these animals both showed some rickets of equal degree. At death, however, after 18½ weeks of feeding, 301 (Fig. 72) had more advanced rickets, while in 300 (Figs. 68 and 71) (casein) curative changes had started. The interpretation of the experiment is, possibly, that casein had but little influence in inhibiting the development of rickets but that, when the puppy became ill and refused to eat its diet, especially the bread, completely, the rate of growth decreased and curative processes were set up at the epiphyseal ends.

It will be noticed that the casein dog (300) at death had a rather less percentage of calcium in its bones than 301 (7·7 per cent. CaO in fresh femur shaft as compared with 9·25 per cent. in control animal). In the section of this paper dealing with the effect of meat protein, an experiment of this series (299) was described wherein it was shown that meat protein improved endochondral calcification but had less effect on the periosteal calcification. These experiments show that edible casein, when substituted for an amount of bread equivalent as regards energy, has but little effect on rickets.

Caseinogen (*acidic in reaction*). I shall now show that an acidic sample of casein (probably ordinary caseinogen made by acid precipitation of milk) has very definite rickets-producing action (see Exps. 321–5). I use the word ' rickets-producing ' in this case because the condition as regards external appearance and radiographic examination was indistinguishable from rickets. There was some osteoporosis as well as rickets. I wish to emphasize that all these animals received an equal and an adequate amount of calcium in the separated milk of the diet so that any osteoporotic condition that may have developed was not equivalent to the state produced by Miwa and Stoeltzner (20) when they fed puppies on diets deficient in calcium. The histological examination of this material shows that the rachitic changes were attended with osteoporosis.

The object of this series of experiments made on five retrievers of the same litter was twofold in the first place.

(1) To test the effect of casein on rickets development and to see whether the removal of any Fat-soluble A from commercial samples of ' casein ' by prolonged extraction with alcohol made a difference to its effect on the production of rachitic changes.

(2) To see whether heating butter 120° C. for 4 hours and passing oxygen through it during this period and so destroying its Fat-soluble A content would destroy its anti-rachitic action.

The second of these points has already been discussed (p. 29), where it was shown that destroying the Fat-soluble A content of butter had a definite effect in inhibiting the calcification of bones of the animals.

General Diet.

Separated milk 175 c.c. Salt 1 grm.
Bread 100 grm. + Lean meat 5 grm.
Orange juice 5–7·5 c.c.

In addition the animals received for 8 weeks the following substances :

321. 5–10 grm. autoclaved and oxidized butter (4 hours).
322. 5–10 grm. fresh butter + 10–20 grm. ' casein ' (unextracted).
323. 5–10 grm. autoclaved and oxidized butter + 10–20 grm. ' casein ' (extracted).
324. 5–10 grm. fresh butter + 10–20 grm. ' casein ' (extracted).
325. 5–10 grm. fresh butter.

After eight weeks of the above diet, the radiographs show the following changes (Figs. 46, 47, 48, 49, and 50).

321—rickets, 322—rickets, 323—very bad rickets, 324—rickets, 325 normal.

The deductions to be made from these results are :

(1) That butter with its Fat-soluble A destroyed allowed rickets to develop more rapidly.

(2) That ' casein ' (acidic), whether it contained its Fat-soluble quota or not, brought about the development of rickets even though fresh butter was eaten. When the butter had its Fat-soluble A destroyed, the addition of casein brought about severe rickets more rapidly.

(3) There is but little evidence of any real difference in the action of casein whether unextracted or extracted with alcohol. Both were detrimental.

Of these puppies, 321 and 323, both receiving the oxidized butter, never completely recovered from the anaesthetic administered for radiographic purposes, and were killed. The CaO in the shafts of the fresh femurs was abnormally low in both cases, 5·9 (321) and 4·1 per cent. (323).

Having seen that this type of ' casein ' hastened the onset of the rachitic condition, it was then removed from the diets of the rachitic dogs to see if recovery would take place and added to the diet of 325 which, up to that stage, had remained normal to see if rickets would develop.

The following alterations were made accordingly in the diets of the three remaining puppies after about 11 weeks of the experiments.

322.   Bread greatly reduced to see whether, by living for a short time on its own fat stores, recovery would take place in spite of the presence of casein.

324.   ' Casein ' cut out altogether ; bread increased to 190 grm. to allow for loss of energy due to removal of casein.

325.   ' Casein ' (15 grm. per diem) added to diet. Bread reduced to 170 grm.

The results of this treatment, as indicated by the radiographs, are as follows :

322.   (Cutting down bread, ' casein ' and butter remaining.) Period of new diet 26 days—weight reduced from 4,910 to 4,390 grm. —puppy remained well. A possible slight attempt at repair resulted.

324.   (Removal of ' casein '.) Calcification at the epiphyses shows some recovery (Fig. 83).

325.   (Addition of ' casein '.) Severe rickets rapidly developed (compare Figs. 50, 86, and 87).

On removing ' casein ' from the above diet calcification processes were resumed to a slight degree at the epiphyses while the addition of casein brought about severe deficiency of calcification.

It has been shown that edible casein (basic) has but little influence on the development of rickets. When substituted for bread with equivalent energy value, little effect was apparent. The experiments with acidic ' casein ' make it clear that this substance depresses calcification processes and hastens rickets even when butter is also eaten. At first these discordant results were most perplexing because it was thought that the casein used in all cases was of the same type. On closer examination it was found that one kind of casein (edible) was alkaline and the second kind acidic. Is the acid attached to the caseinogen the cause of the interference with calcification ? It is possible that this acid removes the calcium and prevents its access to the tissues. I do not know how much acid there was in the acidic caseinogen. It was a commercial preparation and such substances often have a great deal of acid attached because of imperfect washing. Even carefully prepared acid caseinogen has a slight acidic reaction,

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however long it may be washed after precipitation. It has been shown by Götting (21) that adding oxalic acid to the food of puppies will produce osteoporotic changes in bone. This can be readily understood for it would doubtless combine with any calcium salts of the diet in the alimentary canal so that the outcome would be similar to feeding on foodstuffs deficient in calcium. It has also been stated that lactic acid produced from carbohydrate in the intestine by fermentation is responsible for rickets, but I am unaware of any experimental evidence which supports this view. Although the effect of the acid in acid caseinogen cannot be decided except by further experiment, it does not seem likely to be the real explanation of the above-described facts. Otherwise it might be expected that all the dogs receiving orange and lemon juice would develop rickets, which is certainly not the case.

On estimating the calcium present in the two samples of ' casein ', the following results were obtained :

'edible casein' contained 2·4 per cent. CaO.
acidic 'casein' ,, 0 ,, CaO.

The great difference in the various forms of ' casein ' on the market is evident from the work of John Mellanby, who has supplied me with the following facts. Caseinogen as present in milk is a protein calcium phosphate complex of such a nature that 3,600 grm. of protein approximately are associated with one gram molecular weight of $Ca_3(PO_4)_2$. On acid precipitation the calcium phosphate is split off and, not only so, but the protein moiety is also changed by the acid. Some of this acid adheres to the protein portion but can be got rid of by careful washing. If for instance hydrochloric acid is used, the precipitate can be washed until no more chlorine remains. The protein after washing is still slightly acidic and decomposes calcium carbonate with the evolution of CO_2, forming a calcium caseinate of a nature that approximately 7,500 grm. of compound contain 1 grm. molecule of calcium. The acid protein will not combine with calcium phosphate to form the original caseinogen. Acidic caseinogen is in fact an acid owing its acidity no doubt to the arrangement of phosphoric acid in its molecule, and it is most probable that this arrangement is not found in the protein of milk before precipitation.

The protein moiety of caseinogen as found in milk and acid-caseinogen both contain 0·7 per cent. of phosphorus in combination. In milk there is a corresponding amount of calcium. In acid-caseinogen there is no calcium so that the phosphoric acid liberated from it during digestion may be responsible for the deprivation of calcium salts and subsequent defective calcification of bone in the above-described experiments. I have dealt with this question in detail because it is likely that further work will be undertaken by other investigators on the effect of vitamines on calcification processes, and it is obvious how difficult a problem of this nature will be unless the experimenter bears in mind the various actions which may be expected according to the type of ' casein ' used in the synthetic diet.

Further, it is evident how important is the caseinogen calcium balance in milk from the point of view of growth of bone.

Since caseinogen, the more abundant protein in milk, contains a large amount of calcium it is not surprising that there is in animals of different species a close relation between protein and calcium content. The total protein-calcium ratio in milk of different animals is, however, not constant for two reasons : (1) the variable amount of lactalbumen ; (2) the variable amount of free di- and tri-calcium phosphate and calcium chloride. If the interpretation of the foregoing experiments is true, the association of caseinogen and calcium is evidently of great importance from another point of view, for any condition which diminishes the amount of calcium in proportion to the protein of milk may also lead to a disturbance of calcium metabolism favourable to the development of rickets. Further experiments will settle this point.

(ii) Milk-fat.

In dealing with the action of fats, it was remarked that, whereas butter had a stimulating effect on the formation of calcium phosphate in the periosteal bone, occasionally cases of rickets were found where butter was the fat eaten. In these cases defective endochondral ossification was found in bones which subperiosteally were almost normal. Sufficient experiments, perfectly controlled in all detail, have not been made to determine whether butter stands in an exceptional position in this respect as compared with other fats. At first it seemed to me probable that the somewhat discrepant results with butter might be explained by differences in the quality of the butter : when made from summer milk it appeared to be more anti-rachitic than when made from winter milk. Experiments, which will be reported when more data are obtained, were started early in 1919 to test this point. In my experience the problem is more complicated than recent publications dealing with vitamines in milk would indicate.

It is certainly possible to convert a positive calcium balance into a negative balance by an undue increase of butter intake as compared with other foods. In Exp. 155, a puppy eight weeks old was given 15–30 grm. of butter per diem, the rest of the diet being made up of separated milk, bread, and yeast. In spite of the large amount of butter or possibly, because of it, the animal did not flourish and actually lost weight in the experimental period of three months. At the end of this time its bones were very soft and contained only 7·8 per cent. of CaO. There was no indication of rickets revealed by histological examination of the bones. The large amount of butter in the diet had increased the rate of excretion of calcium salts.

It is possible that excess of butter only converts a positive calcium balance into a negative one when it causes a dyspeptic condition to develop. This happened in Exp. 155 described above, where the bones became very soft with a small content of calcium.

That butter in excess has under some conditions the power of increasing the excretion of calcium, and thereby creating a negative balance, is also supported by the experiment of Rothberg (22), Steinitz (23), and Meyer (24). On the other hand Telfer's (25) recent results are contrary to these former workers, for he showed that increasing the butter intake from 21·6 grm. to 43·2 grm.

per diem over periods of five days did not affect the calcium retention in a child. There is probably some simple explanation of the discrepancy between these results because of the general agreement among all the German workers, and it is difficult to imagine serious errors in calcium estimations.

In any case the foregoing type of investigation does not seriously affect either one way or another the work described in this paper, for the period of a few days—three up to seven—during which the metabolic changes were examined by the various researchers is probably too short to lead to results bearing upon the subject of vitamines—at least so far as fats are concerned. For in dealing with the question of fats and the anti-rachitic vitamine, it was evident that several weeks usually passed before a diet deficient in anti-rachitic vitamine showed any obvious effect on calcification when given to a healthy animal.

I have made a few experiments to see whether butter has a greater anti-rachitic action if the calcium intake is increased at the same time. Although this portion of the work is still very incomplete, there is some evidence that butter and calcium salts have a synergistic action in opposing or curing rickets. In dealing with the casein-calcium balance in a preceding section, it was seen that, although butter was eaten, great defect in calcification was produced when ' casein ' (acid caseinogen) was added to the diet, and when this protein was removed, attempts at repair and renewed calcification became evident. The rate of this improvement was slow (Exp. 324), and the animal became partially paralysed in its hind limbs. The diet at this period was separated milk 200 c.c., bread 190 grm., butter 15 grm., meat 10 grm., lemon juice 7·5 c.c. On October 12 whey made from 450 c.c. of milk was added to the diet, and by December 1 the rickets was greatly improved (see Fig. 85, taken Nov. 18). The paralytic condition also rapidly disappeared (compare Figs. 84 and 85).

In another puppy of the same series (325) which had bad rickets, having previously eaten ' casein ' (acid caseinogen), the ' casein ' was removed from the diet and the ash of 45 grm. of separated milk powder added. In six weeks curative processes had been well started. This puppy was also partially paralysed before the salts of milk were added and quickly recovered after their addition (compare Figs. 87 and 88). 322 (same series as 324 and 325), casein (acid caseinogen) was removed from the diet, when advanced, though possibly healing, rickets was present, and 45 grm. of dried separated milk powder substituted for it. In this case the curative processes continued (Figs. 81 and 82). A synopsis of the above curative experiments is as follows :

3 retrievers with bad rickets received.

General Diet :

Separated milk 200 c.c.   Bread 150–190 grm.
Butter 15 grm.   Lemon juice 7·5 c.c.

322	324	325
Dried separated milk powder 45 grm.	Whey from 450 c.c. separated milk.	Ash from 45 grm. separated milk powder.

All puppies showed curative changes in six weeks. As compared with the curative changes resulting from the removal of the acid-caseinogen only, it appeared as if the addition of calcium salts either in separated milk powder, whey, or the salts of separated milk powder had hastened the establishment of calcification changes apparent at points of endochondral ossification. These curative changes described above took place although the animals were closely confined, and in two cases the puppies were also paralysed. The paralysis disappeared on change of diet.

These experimental results indicate that butter is a more potent anti-rachitic agent when it has abundance of calcium salts, as found in milk, with which to work. It is but natural that the anti-rachitic vitamine of butter, which certainly has a strong influence on the deposition of calcium phosphate in bone, should also have a sufficiency of calcium salts in the diet before it can work effectively. That it should be necessary to balance closely the intake of butter and calcium salts, so that increase of the former must be accompanied by increase of the latter in order to produce the greatest anti-rachitic effect is not so obvious. The above described results, however, suggest that milk is a foodstuff which is naturally made up of well-balanced constituents, and any artificial changes in the relative proportions of its elements, such as are so commonly carried out for purposes of infant feeding, can only be a safe procedure when our knowledge of this foodstuff is much greater than it is at present.

Summary.

(1) Evidence is offered tending to show that, when casein containing calcium is added to the diet, it has very little effect on rickets. When acid-caseinogen containing little or no calcium is eaten, great defect in calcification of bones is produced, even when the diet contains butter. It is possible that the close relation between the amounts of protein and calcium found in milk of animals of different species is of some importance from the point of view of milk as an article of diet for young animals, and the development of rachitic changes in these animals.

(2) The action of the anti-rachitic vitamine in butter is apparently more effective when there is also abundance of calcium salts in the diet.

(3) These results emphasize the inadvisability of altering the relative proportion of milk constituents in the feeding of infants, until our knowledge of the actions of these components and their interactions with one another are more perfectly understood. To increase either the caseinogen or butter element without at the same time increasing the calcium salts is contraindicated by these experiments. The whole question requires further investigation.

(f) The Relation of Calcium to the Anti-rachitic Vitamine in Foodstuffs.

I wish now to discuss briefly the part played by calcium salts in the diet, and their relation to rickets and conditions simulating rickets.

In the first place the diet must certainly contain a sufficiency of calcium. In the popular mind, and even among medical men and

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scientific workers, there is a strong belief that rickets is due to a deficient calcium intake in the food. It may often be an adjuvant factor in the production of rickets, and if other conditions conducive to the disease are present, a deficient calcium intake will certainly exaggerate the signs and hasten the onset of rickets. On the other hand, experimental work has clearly shown that calcium deficiency in the diet alone will not produce rickets. Miwa and Stoeltzner (20) fed puppies on horse flesh and distilled water—a diet very poor in calcium. The changes in endochondral ossification were small, but there was very evident osteoporosis in the shafts of the bone. Götting (21) also produced osteoporotic changes as the result of giving diets poor in calcium. Dibbelt's (9) results are more interesting from the point of view of this research. He fed puppies on horse flesh and fat, and on horse flesh and carbohydrate. In all cases osteoporosis was produced, but when horse flesh and carbohydrate were eaten, there was also an increased amount of ' osteoid tissue '. When fat was eaten with horse flesh, the osteoid tissue was greatly diminished. There seems no doubt that Dibbelt produced a combination of rickets and osteoporosis when there was no fat and anti-rachitic vitamine in the diet, and osteoporosis only when the fat and its vitamine content was eaten. Whether, therefore, osteoporosis or a combination of rickets and osteoporosis develops on diets poor in calcium depends partly on the deficiency in calcium and partly on the other constituents of the diet, excess of carbohydrate favouring the production of osteoid tissue, while the proper type of fat exerts its influence by regulating the correct calcification and structure of any bone that may be laid down.

Just as it is certain that deficiency of calcium alone will not produce rickets, clinical and experimental observations are equally conclusive that abundance of calcium in the diet will not prevent rickets. Certainly the addition of calcium phosphate to a rickets-producing diet will not prevent rickets. In Exp. 122, the puppy (six weeks old) was given 5 grm. of $Ca_3(PO_4)_2$ daily in addition to a diet of 175 c.c. separated milk, white bread ad lib., and 10 c.c. linseed oil. Its weight increased from 1,800 grm. to 3,170 grm. in ten weeks. Bad rickets had developed in this time, and the experiment was stopped after thirteen and a half weeks of the diet. The calcium oxide present in the fresh shaft of femur was 9·3 per cent., and histological examination revealed advanced rickets.

Although the calcium intake cannot be considered a crucial point in the case of rickets, its importance in the dietary can be easily overlooked, for it is a matter of great ease to choose a diet in which the calcium intake is remarkably low. A diet of this nature would include all forms of meat, white bread, margarines and most other fats, sugar, potatoes, polished rice and many manufactured cereals. These substances form the basis of the normal diets of many people, especially the poor in this country, and it would be surprising if a deficient calcium intake were not a very common defect. The amount of calcium reckoned as calcium oxide is found in the following foodstuffs : [1]

[1] Figures calculated from those of Albu and Neuberg (*Mineralstoffwechsel*, Berlin, 1906).

Meat .	.	.	.	0·015 CaO
White bread	.	.	less than 0·014
Sugar.	.	.	.	none
Margarine .	.	.	none
Potato	.	.	.	0·025
Polished rice	.	.	0·016

Cow's milk	.	.	.	0·16 CaO
Egg yolk	.	.	.	0·4
Cabbage .	.	.	.	0·45
Cauliflower	.	.	.	0·14
Butter .	.	.	.	0·37
Oatmeal .	.	.	.	0·12

In this table I have contrasted the foodstuffs containing abundant calcium with those with very little calcium.

Even assuming that foodstuffs are passive as regards calcium metabolism, so that all the calcium salts absorbed from the intestines are stored up in the body, it is obviously easy, especially in those places where the water is almost free from calcium salts, to eat a diet which can only result in the defective calcification of bone. The osteoporotic condition that develops in dogs from a deficient lime intake produces an external appearance identical with rickets. It seems to me probable that deficient calcium in the food may play a more important part in the aetiology of rickets—more especially in late rickets so common nowadays—than is sometimes assumed. For it is obvious that, however favourable the diet and metabolic conditions may be, they must be inadequate from this point of view if there is little or no calcium absorbed. On the other hand, if other dietetic conditions favour the production of rickets, a deficiency of calcium in the food will emphasize the pathological changes.

What then is an adequate calcium intake ? There is no absolute amount that can be described as adequate, because the amount necessary for the production of perfect calcification has been seen to depend on the other elements of the diet and environment, some of these factors helping the cells of the body to make use of calcium while others prevent this action. It is all a question of balance.

It is a most fortunate occurrence that nature has so ordered matters that if an attempt be made to eat foodstuffs containing an abundance of calcium, those substances generally also contain a large amount of the anti-rachitic vitamine, or, in any case, the Fat-soluble A vitamine. Milk and egg yolk contain a large quantity both of calcium salts and anti-rachitic factor. Cabbage and other green vegetables are very rich in calcium and also Fat-Soluble A—in fact green leaves are undoubtedly the original source of this vitamine. It has so far not been possible in this investigation to carry out successfully any experiments on dogs to decide whether green leaves have a potent anti-rachitic effect, but it can be prophesied with some safety that this will prove to be the case. The opposite condition also holds with many of the commoner natural foodstuffs, for those that contain no anti-rachitic vitamine so far as our present knowledge goes also have a low calcium content. Not only, therefore, do the experimental results obtained in this research point to a close interworking between the anti-rachitic vitamine and calcium salts, but also their distribution in nature would give support to the same view.

SUMMARY.

An analysis of ordinary articles of diet shows the ease with which diets deficient in calcium can be chosen. Although a deficient intake of calcium alone is not the cause of rickets it is probable that this is

a common cause of exaggerated signs and symptoms in the disease, and more particularly in late rickets.

The choice of a diet rich in calcium, e. g. milk, egg yolk, and green vegetables, fortunately leads to the ingestion of an abundance of Fat-soluble A, and substances deficient in one are usually deficient in the other. This distribution in nature indicates a close interaction of these two substances, and supports the experimental results obtained.

V. THE PART PLAYED BY EXERCISE AND CONFINEMENT IN THE AETIOLOGY OF RICKETS, AND THEIR RELATIVE IMPORTANCE AS COMPARED WITH DIET.

Mainly as the result of observations made on wild animals when confined in zoological gardens, Hansemann (31) suggested the ' domestication ' hypothesis as the cause of rickets. ' Domestication ' factors included various conditions such as confinement, lack of exercise, and absence of fresh air, and was too comprehensive to convey much meaning. The hypothesis was narrowed down by Findlay (13), following some experimental work on the development of rickets in puppies, which, while remaining on the same diet of porridge and milk, were either confined to rooms in the laboratory or allowed to run about and take exercise in the open. The experimental results were in favour of confinement being the real cause of rickets. Findlay's experiments I have criticized elsewhere, and it only remains to state here that, in my opinion, the diets were neither good enough nor sufficiently controlled to allow of the important conclusion that lack of exercise alone is the cause of rickets in children. The experiments on the effect of confinement were repeated by Paton, Findlay, and Watson (26), and the results obtained were in agreement with those of the earlier work. In these latter experiments the diets were more closely controlled, and attention was paid to my previously published conclusion that a vitamine of the nature and distribution of Fat-soluble A played a part in the aetiology of rickets. These workers got no evidence that such was the case, and the main factor influencing the development of rickets in their experiment was exercise.

In addition to animal experiments, a large enquiry into the cause of rickets in children was carried out in Glasgow by Ferguson (32), Findlay, and Paton, a great deal of data as to housing and diet being collected in order to discover why some families were rachitic and others normal. The conclusions reached in this investigation were in agreement with their previous animal experimental results, for it was found that there was close correlation between the number and size of rooms used for habitation and incidence of rickets, and no evidence of a dietetic factor playing a part in rickets was obtained. This research I have also criticized elsewhere (1 and 2).

As the result of the two types of work carried out in Glasgow, Findlay has come to the conclusion that lack of exercise is the cause of rickets. Paton now disagrees with Findlay that exercise plays this predominant part, and thinks there is some other factor possibly

of an infective nature to be considered. This latter view he does not deduce from his own experiments only, but lays stress on the observations of Bull, who described an ' epidemic ' of rickets among foxhound puppies, the only certain cure of which was to remove the puppies to some part of the property where they had not previously been. It ought to be added that Bull (29) thinks diet also of importance, and states that he believes that ' had more opportunity occurred of improving the diet, the disease would have been completely controlled '. The infective hypothesis of rickets has been advanced by others, including Morpurgo (35), J. Koch (27) and Marfan (28), and I shall discuss it later. At this point I may say that I do not consider that infection has anything to do with rickets in a normal way, but it may hasten the development of symptoms and exaggerate the disease if the other rickets-producing conditions are present.

As regards the effect of confinement and exercise, I shall now show that, although exercise has an undoubted anti-rachitic action in the case of puppies, its importance is quite subsidiary to diet, and that even the possibility of taking exercise is dependent on diet.

The effect of confinement on the development of rickets was one of the first things tried in this research, at a time when I had no ideas as to the causative factors. It will be noted that the earlier experiments are crude in that no quantitative data are known as to the different constituents of the diet eaten. On the other hand, the conditions of confinement were strenuous, and the complete absence of rickets in these puppies led me to the conclusion that confinement did not hold the important position in the aetiology of rickets that Findlay had ascribed to it.

In later experiments full details of diet are given, and with variation of diet it is possible to see in better perspective the relation between confinement and diet in the development of rickets. The subject is by no means fully worked out, but sufficient data are at hand to afford the opportunity of appraising the value of these two factors.

Experimental work has been carried out on various lines, including the following :

1. Puppies have been confined but allowed a good diet. They have not developed rickets.
2. Puppies have been allowed complete freedom during the daytime, but the diet has been defective. In all cases these puppies have developed rickets. Only one has remained almost normal. This puppy was of a small breed, ate but little food and grew very slowly during the experimental period.
3. Animals have been given rickets and later have been confined, while at the same time the diet has been altered so as to contain a supply of anti-rachitic vitamine. It will be seen that in spite of confinement curative processes started.

Each of these points will be treated in turn.

(a) **The Absence of Rickets during Confinement on a good Diet.**

In the earliest experiments which were made on this point four puppies were placed on the following diets :

(a) Bread, milk and meat.
(b)   ,,   ,,   ,,   and bone.
(c)   ,,   ,,   ,,   and bone that had been autoclaved (120° C. for a quarter of an hour).
(d) Bread, milk and meat and calcium phosphate (10 grm. per diem).

The animals were confined absolutely in kennels 3 ft. 6 in. by 2 ft. 6 in. They were 10 to 12 weeks old at the commencement of the experiment and after 13 weeks confinement were killed (Exp. 25, 26, 27, 28).

No. of experiment.	Initial weight. grm.	Final weight. grm.	Calcium oxide in dry bone. %
25	3,280	4,438	42·92
26	4,280	6,680	38·13
27	3,300	6,460	37·46
28	2,810	4,030	30

Histologically no sign of rickets could be seen. Chemical examination revealed the calcium content of the shafts of the bones to be high.

The criticism against these experiments is that the animals were 10 to 12 weeks old at the beginning of the experiment. Had the confinement delayed calcification, however, there would have been evidence of this in the smaller calcium content of the shaft of the bone (*vide* Exp. 264, 265, 266, and 267, p. 26).

The following Exp. 29, 31, and 32 were carried out on similar lines. Puppies 31 and 32 were of the same family.

Exp. 29. *Diet.* Bread.
Milk.
Meat.
Length of experiment. 18 weeks.
Initial weight. 2,255 grm.
Final weight. 7,150 grm.
Calcium oxide in dry bone. 35·84 per cent.
Histology of bones. Normal.

Exp. 31. *Age.* 8 weeks old at beginning of experiment.
Diet. Bread.   Changed after 13 weeks to :
Milk.   Bread.
Meat.   Milk.
Calcium phosphate.   Melox.
Length of experiment. 22 weeks.
Initial weight. 2,150 grm.
Final weight. 6,810 grm.
Calcium oxide in dry bone. 36·64 per cent.
Histology. Normal.

Exp. 32. *Age.* 8 weeks old at beginning of experiment.
Diet. Bread.
Milk.
Meat.
Autoclaved bone.

Length of experiment. 22 weeks.
Initial weight. 2,708 grm.
Final weight. 6,580 grm.
Calcium oxide in dry bone. 32·36 per cent.
Histology of bones. Normal.

In the following experiments the diets were more closely controlled.

Exp. 156. *Age.* 5 weeks old at beginning of experiment.
Diet. Whole milk 300 c.c. Raised to 400 c.c. after 10 weeks confinement.
Meat 50 grm.
Yeast 10 grm.
Wheaten bread 70 per cent.
Linseed oil 5 c.c.
Length of experiment. 18 weeks.
Initial weight. 1,695 grm.
Final weight. 6,660 grm.
Calcium oxide in dry bone. 25·40 per cent.
Calcium oxide in fresh bone. 17 per cent.

No rickets. Histological examination shows bone normal.

Exp. 190. *Age.* 6 weeks.
Diet. Bread *ad lib.*
Yeast 5 grm.
Salt 1 grm.
Orange juice 3 c.c.
Separated milk 175–250 c.c.
Cod-liver oil 10 c.c.
Length of confinement. 7 weeks.
Initial weight. 1,325 grm.
Weight after 7 weeks. 2,315 grm. Legs bent early in experiment owing to the loosening of the ligaments. Animal ran very well and was lively.

Radiograph at this period shows normal bones (Fig. 10).

Radiographs of 186, 187, and 189, puppies of the same litter as 190 kept under the same conditions, of which 186 had linseed oil, 187 had cotton-seed oil, 189 had peanut oil, show that during this period of confinement they had developed rickets (Figs. 7, 8, 9).

CaO in fresh bone 14·5 per cent.

Note.—In Exp. 190 the diet contains no *Meat.*

Exp. 198. *Age.* 8 weeks at beginning of experiment.
Diet. Bread *ad lib.*
Whole milk 250 c.c.
Meat 20 grm.
Cod-liver oil 5 c.c.
Orange juice 5 c.c.
Salt 1 grm.
Length of Confinement. 13 weeks. At the end of this time the legs were quite straight and the X-ray photograph was normal (Fig. 89). Animal runs well. A photograph of this puppy is shown in Fig. 90.
Initial weight. 1,405 grm.
Weight after 13 weeks. 5,925 grm.

This puppy did not develop the loose ligaments seen in the previous experiment (190) and, throughout the period of confinement, remained a fine healthy animal with a beautifully glossy coat.

Exp. 350.   8 weeks old at beginning of experiment.
        Diet.   Whole milk 200 c.c.
            Melox 50–150 grm.
            Meat 20 grm.
        Length of confinement.   14 weeks.
        Initial weight.   1,280 grm.
        Weight after 14 *weeks.*   4,000 grms.
Radiograph (Fig. 113) is normal.
This animal is still alive and is in perfect health.

Here we have a number of experiments carried out with confined animals. In all cases the diets contained abundant anti-rachitic factor, and except for the slight looseness of the ligaments seen in 190, which was otherwise a normal puppy, there has been no suggestion of the development of rickets. On the whole it will be seen that the animals grew well and kept in perfect condition.

(*b*) Development of Rickets when Exercise is allowed on a Defective Diet.

Exp. 192.⎫ Terriers.
    193.⎭
        Diet.   Bread *ad lib.*
            Yeast 5 grm.
            Salt 1 grm.
            Orange juice 3–5 c.c.
            Separated milk 250 c.c.
            Linseed oil 10 c.c.

Of these two puppies 192 was allowed complete freedom during the day, 193 was confined.

It will be noticed that the diet in these two experiments was of a ricket-producing nature.

Initial weights. 192.   1,980 grm.   *Final weights.* 192.   3,275 grm.
            193.   1,450 grm.   193.   2,660 grm.
        Length of experiment.   19 weeks in both cases.

X-ray photographs taken after 17 weeks of diet show that both puppies had developed rickets, 193 (Fig. 95) (no exercise) being worse than 192 (Fig. 96).

The deduction from these experiments and others of the same type is that confinement has made the condition worse, but that, even with the full possibility of exercise, well marked characteristic signs of rickets developed. Both these dogs were ill towards the latter end of the experiment and 193 died. A similar outcome would probably have resulted in 192 had not the diet been altered by substituting cod-liver oil for linseed oil and the addition of 50 grm. of meat for a few days. The subsequent history of this dog 192 is referred to elsewhere (p. 65).

Exp. 199.   This puppy was of the same family as 198 (*vide supra*); both being terriers.

Animal allowed complete freedom.

Age.   8 weeks at the beginning of experiment.

Diet.   Bread *ad lib.*
Yeast 5 grm.
Salt 1 grm.
Orange juice 5 c.c.
Linseed oil 10 c.c.
Separated milk 250 c.c.
Marmite 1 grm.

Length of experiment.   19 weeks.

Initial weight.   1,485 grm.

Final weight.   4,440 grm.

A series of radiographs of the wrist of this puppy are shown (Figs. 92, 93, and 94). It will be seen that rickets developed after 10 weeks. During the continuation of the experiment under the same conditions, the radiographs show improvement in the rachitic condition. This is an instance of self cure occurring while the animal remained on the same diet. Possibly the larger amount of separated milk given to this animal played some part in recovery.

Calcium oxide in fresh femur (after healing process at epiphyses established), 6·91 per cent.

In spite of the healing process, evident in the radiographs, the calcium in the bones has remained very low. The amount of rickets was certainly not very profound, but on the other hand, the dog was of a small type which grew slowly as compared with 198. The dog's bones were bent to some extent and its external appearance was distinctly rachitic. It must be doubted, however, whether the healing process would have started and continued in this fashion, had not the dog been allowed complete freedom. The very low calcium content of the bone, which apparently did not increase to any extent, in spite of the healing changes evident at the epiphyses, emphasizes the danger of laying too much stress on radiographic examination as evidence of cure. That the condition, as the result of the continuation of the experiment, improved, is undoubted, but the small amount of calcium oxide present in the shaft of the bone, indicates that the improved conditions of calcification that were resumed after the disease had developed were slight in quality and did not have sufficient time to affect the periosteal bone.

Exp. 165.   In this case also the dog was allowed freedom and took much exercise during the experimental period.

Small terrier breed of dog.

Age.   8 weeks old at beginning of experiment.

Diet.   Bread 70 per cent. *ad lib.*
Separated milk 175–250 c.c.
Linseed oil 10 c.c.
Yeast 10 grm.
Orange juice 5 c.c.
Meat occasionally.

Length of experiment. 17 weeks.
Initial weight. 1,330 grm.
Final weight. 2,900 grm.

In the eleventh week of the experiment the animal's weight was only 2,200 grm.

This animal had only slight rickets when examined histologically.
Calcium content in dry bone. 29 per cent.
Calcium content in fresh femur. 18·85 per cent.

Exp. 164. As compared with a brother of the same litter, 165, which also did not grow much, the exercised dog was certainly more normal. 164 was on a similar diet to 165 but was kept confined throughout the experimental period.
Initial weight. 1,340 grm.
Final weight. 2,300 grm.
Maximum weight. 2,475 grm.
Histological examination shows it to have rickets.
Calcium content in dry bone. 17·9 per cent.
Calcium content of fresh femur. 10·7 per cent.

In comparing these two dogs 164 and 165 it is clear that the exercise has retarded the development of rickets. The smallness of the dog (165) and the slight rate of growth would, from previous experience, indicate that no great accessory influence would be necessary in this case to turn the balance from the rachitic to the non-rachitic condition. The amount of exercise received by the dog was apparently of sufficiently great influence to keep it almost normal from the rickets point of view. It was most difficult, especially in the first ten weeks of the experiment, to get these dogs, particularly 165, to eat their food. 165 drank the separated milk with avidity, but preferred, as a rule, to leave the rest of its food.

Exp. 251.
     252. } These were retriever puppies.

Age. 6 weeks old at start of experiment.
251 and 252 were put on the following diet :
          Bread 100–200 grm.
          Separated milk 175–250 c.c.
          Yeast 10 grm.
          Orange juice 5 c.c.
          Linseed oil 10 c.c.
          Meat 10 grm.
251 had no exercise, 252 was out continuously in the open air.
Initial weights. 251. 2,180 grm.
                252. 2,210 grm.
Weight after 9 weeks. 251. 5,020 grm.
                   252. 4,875 grm.

Radiographs of these puppies taken after nine weeks of the diet are shown, and it will be seen that both have developed advanced rickets, but that of the two, 251 (Fig. 102) (no exercise) is worse than 252 (Fig. 104).

In this case we see, again, that exercise has had an improving

effect on the condition so far as radiographic examination is concerned, but that unlike 165, where we were dealing with a small type of puppy eating very little bread, the exercise obtained in this case has not prevented the development of bad rickets.

In the above described experiments made to test the effect of exercise and confinement, meat usually formed an element of the diet in the confined animals and was absent in that of the exercised animals. In Findlay's experiments (13) and in the later work of Paton, Findlay, and Watson (26), no meat was eaten. It seemed possible that some part of the discrepancy between our results might be due to the presence and absence of meat in the respective experiments. In another section of this paper I have dealt with the action of meat in rickets and shown it to be definitely but slightly anti-rachitic, this action being more noticeable as regards endochondral calcification than calcification of periosteal bone when the diet is deficient in the anti-rachitic vitamine.

It is of interest to note in this connexion that Lehnerdt (30), working on the effect of confinement, also came to the conclusion that it was not the cause of rickets. The account of his work is brief and contains but little detail. Of six puppies, five weeks old, three were allowed a two-hours' run daily in a garden and, at other times, were closely confined together with the remaining three which got no opportunity for exercise. After some months of this treatment no evident rickets was produced in any of the dogs. The bones of the confined animals were hard and macroscopically showed no rachitic changes. Microscopically they were not examined. The food eaten by the puppies consisted of milk, meat, and bread, and each puppy was given 1 grm. of calcium phosphate daily. It will be noticed that this diet differs from that used by Findlay in that it contained meat and is, in fact, the same diet as that used in my earlier experiments, when confinement did not produce rickets.

In the section dealing with meat I have described experiments made with the object of seeing what is the effect of adding meat to a rickets-producing diet when animals are confined, and when allowed full freedom during the daytime (with muzzles on) (see Exp. 351, 352, 353, and 354). Experiments on diet and exercise are useless unless the puppies are muzzled. Instinct leads them to know what their diets lack and they will make good this deficiency if given the opportunity. Of these animals 351 and 352 were allowed freedom, 353 and 354 were confined. The diets were exactly the same, quantitatively and qualitatively, in all the dogs except that 351 (exercise) and 353 (confined) were given an extra ration of lean meat (20–30 grm.) per diem. After eight weeks both the puppies getting no meat, confined and with exercise (352 and 354), developed rickets, easily recognizable in the radiographs, Figs. 63 and 65. Neither of the meat-eating puppies (351 and 353) showed definite rickets by radiograph at this stage of the experiment (Figs. 62 and 64). The anti-rachitic effect of the meat is evident both when the animals are confined and allowed exercise. It may be added that, throughout the whole experiment, all these puppies lived out of doors. The effect of adding meat to the diets requires further comment. The difference in the behaviour of the two free puppies

(351 and 352) was most noticeable, 351 (meat) ran about all over the laboratory grounds and showed great interest in the activity of the workers, following them from place to place. 352 (no meat), although given the same facilities as 351, developed a striking lethargy in contrast to 351, and unless stirred up to make an effort preferred to meander slowly round. No better example could be seen of the dominant effect of diet in controlling the activity of an animal.

As regards the confined puppies (353 and 354) neither of these were capable of running, and at first sight 353 (meat) looked as rachitic as 354 (no meat), the legs of both being bent. A closer examination, however, soon revealed that the bending of the legs of 353 was largely ligamentous and that, in contrast with 354, there were no obvious epiphyseal swellings of the leg bones.

The weight curves of these four animals seen in Fig. 66 show that the diets were closely controlled. We see from these results (351, 352, 353, and 354) that

(1) Complete freedom during the daytime has not prevented severe rickets from developing (352).
(2) Meat had a definite anti-rachitic effect both when the animals were confined and when taking exercise.

It is evident that the presence of meat in the diet may explain some of the discrepancies between the various results obtained by different workers on the effect of confinement. I have shown, however, in dealing with this anti-rachitic action of meat that it is small, and bad rickets can be produced in quickly growing puppies even when 50 grm. of lean meat are eaten daily if the diet is otherwise bad.

There seems to be something in common between the anti-rachitic effect of meat and exercise. When the animals are on poor diets (with abundant bread and deficient in foods containing the anti-rachitic vitamine) neither exercise nor meat singly seem to have any potent effect. Acting together, even when the diet is poor, their effect is much more strongly anti-rachitic. With moderate diets, both meat and exercise are capable of putting the animal into a safe position.

In some experiments the animals have not been allowed either meat or exercise and no rickets has developed. The diets in these cases have contained plenty of the anti-rachitic vitamine and calcium salts ; the bread has usually been kept low. During the past year it has been my custom to keep all the puppies confined to their kennels, except when the effect of exercise has been tried, and, if confinement holds the important position in producing rickets that some think, none of my experimental puppies during this period ought to have escaped the disease. This, of course, is not the case.

(c) The Curative Effect of Substances containing the Anti-rachitic Vitamine when the Animals are confined.

It has been pointed out above that as the animals grow older curative changes are sometimes set up in rachitic bones without any change in the diet. It must, therefore, be a matter of difficulty to decide what part age in itself, as compared with alteration in the

diet, plays in any curative changes that may be obvious. In the cases already mentioned, where radiographic examination makes it clear that calcification at the epiphyses has resumed and improvement followed without change of diet, the extent of the rachitic changes, although undoubted, were not excessive.

In order to reduce the curative effect that attaches to increasing age to its lowest limit I have taken two precautions :

1. The animals chosen had rickets, generally of a very severe nature.

2. During the period when the effects of an element of a diet were being tested, the animals were kept confined, so as to eliminate any beneficial effect which we have already seen exercise to have. In several of the animals the rickets was so bad when the curative diets were given that they were completely immobilized by paretic hind legs.

The effect of Milk. The beneficial effect of milk on the disease of rickets can be well seen in Exp. 220. The radiograph (Fig. 15) of this animal shows it to be a case of extreme rickets. One month after the previous radiograph the second photo was taken (Fig. 16). In the short period of one month the curative process has been obviously started and calcification changes have been resumed at the epiphyses. This change is synchronous with the exchange of whole milk for the separated milk previously in the diet.

Exp. 192. This dog also developed rickets while on a rickets-producing diet containing linseed oil. The experiment has been described in an earlier section on the effect of exercise (see p. 60), for this animal developed rickets while being allowed exercise. The diet was changed, cod-liver oil being substituted for linseed oil. 50 grm. of meat were also added for a few days and then reduced to 20 grm.

The effect of making this alteration in the diet was almost instantaneous. The animal became much more lively and the curative process in the bones commenced. These curative changes can be seen by comparing the radiographs of Figs. 96, 97, and 98. This animal was not confined during the curative period, but at the beginning of the cure it was almost incapable of movement.

The effect of Egg Yolk as compared with Egg White.

Exp. 250, 251, 252. All developed severe rickets in the course of an experiment (Figs. 100, 102, and 104).

Two months after the beginning of the experiment, the yolks of two eggs were added to the diet of 250, the white of two eggs to the diet of 251, while that of 252 remained unaltered, viz. the control rickets-producing diet without addition.

A series of radiographs of these three puppies (Figs. 100, 101, 102, 103, 104, 105) shows that the egg yolks have resulted in the recommencement of calcification processes in the case of 250. 251, with the addition of egg-white, remained in a stationary rachitic condition. 252 on the rickets-producing diet steadily grew worse.

We must assume from this experiment that egg-yolk contains an abundance of anti-rachitic vitamine, but that egg-white is free from this substance.

The effect of Cod-liver Oil.

Exp. 205. A greyhound puppy was put on 15 c.c. of cod-liver oil per diem instead of linseed oil, after it had developed severe rickets (Fig. 106). It was also kept indoors in a cage and got no exercise. The curative changes resulting from this alteration in diet were immediate, as can be seen from the radiograph of Fig. 107.

The effect of Butter.

Exp. 213. This puppy developed rickets on a diet in which crude rape oil was the essential fat (Fig. 108).

After about fourteen weeks of the rickets-producing diet, 20 grm. of butter per diem were substituted for the rape oil. Here again it will be seen from the radiographs of Figs. 108 and 109 that curative changes followed on the alteration of the diet by the substitution of butter for the crude rape oil.

Reviewing all these changes described above it would appear that certain articles of diet are able to bring about a profound improvement in the rachitic condition, even when exercise ceases to be an element of importance and where it is highly probable the animals would have died, possibly of extraneous disease, had not the food-stuffs eaten been changed.

The substances having a curative effect include whole milk, meat, yolk of egg, butter, and cod-liver oil. The curative changes described above are doubtless due to the alteration in diet and not to any extraneous factor. It is remarkable how rapidly curative changes commence, so that even in one month in most cases there is considerable renewal of calcification at the epiphyses. How long it would take to bring about hardening of the periosteal bone cannot be stated, but it is probable that this change is a slower one. It is certainly true that renewed calcification of the epiphyses of rickety bone is a rapid and delicate process which can be effected in the curative direction very readily by diet.

Experiments described in this section show that :

(1) Puppies on good diets containing abundant milk, cod-liver oil, and meat have not developed rickets in spite of strenuous confinement.

(2) Puppies when allowed freedom during the daytime have developed rickets when the diet has been strongly rickets-producing, i.e. consisting of bread, orange juice, yeast, linseed oil, and a limited amount of separated milk.

(3) Puppies with very bad rickets have had calcification processes of a curative nature set up at the ends of their long bones even when confined, by the addition to their diets of whole milk, butter, cod-liver oil, and egg-yolk.

(4) Even the amount of exercise a puppy takes depends on the adequacy of the diet from the qualitative point of view.

In view of these results, therefore, I suggest that the rickets-producing influence of confinement is of secondary importance to the effect of defective diets, even in the case of puppies. When the disease is considered in relation to children, any general review of the facts only emphasizes the relative importance of the dietetic as

compared with the confinement factor. In this consideration the following points may be suggested :

(1) During infancy and the period of life in which rickets most frequently develops, a child spends a large part of its time in sleep. Up to the age of one it can only make the most limited movements, and the exercise it gets consists of its small movements, including restlessness and crying. During this period, as indeed throughout life, its general activity depends on the adequacy of its feeding and not on the amount of space wherein it can move about. If due to lack of exercise no child ought to escape rickets, more especially those children of the well-to-do who spend most of their days in cots, nurse's arms, and perambulators. It is indeed curious that symptoms of rickets usually become more prominent after the age of one, at which time the average child is capable of moving about and therefore gets more exercise.

(2) It will be agreed that, although rickets is more rife to-day than at any period in the world's history, conditions of housing are certainly not worse now than they have been. If the exercise a child gets depends on the size of house it occupies, then rickets ought to be less now than in our ancestors' time when the conditions of housing and general hygiene were infinitely worse.

(3) As I have pointed out elsewhere (2) dreadful housing conditions and most unhygienic surroundings are found in the Island of Lewis in the Hebrides. Not only so, but the children rarely leave the 'Black' houses in these Islands until they can walk at the age of about one year. In spite of the unhygienic conditions and lack of exercise and fresh air at an early age, the children of these islands are free from rickets, having very good teeth and an abnormally low infant mortality. Between the ages of one and five the mortality is high, largely due to tuberculosis. The same conditions surround Esquimaux children, and here again rickets is absent and splendid teeth are developed. In both of these instances the diet of the people contains much anti-rachitic vitamine, because of the amount of fish and blubber eaten. Of great importance also is the fact that the children are breast-fed.

(4) No sudden cessation of exercise *per se* can explain the extraordinary amount and severity of rickets that has recently developed in Vienna and other towns in Central Europe in consequence of the war. The problem is obviously a dietetic one and depends largely no doubt on the absence of fats and milk in these countries. It is true that the children are described as lethargic, but the lethargy and lack of growth must be secondary to the abnormally bad dietetic conditions.

I have dealt with the anti-rachitic effect of exercise and its relation to rickets in some detail because, although it is obviously an important factor, it would be calamitous if exercise alone were

regarded as giving immunity to rickets or if it were supposed that a solution of the housing problem were going to eradicate rickets from our midst and confer on the people sound teeth. The housing of all people under good conditions with greatly improved hygienic surroundings is a desirable object, but the real solution to these problems of health is without doubt prominently dietetic. A good diet will itself increase the activity of the young, whereas a rickets-producing diet made up of much bread and little milk will take away any tendency to great activity that an animal may exhibit.

The fact that exercise should have some anti-rachitic action is in physiological accord with the dietetic effect described above, and does not, to my mind, involve the break in continuity that some people imagine. As regards the diet, two outstanding factors are prominent, viz. :

(1) That some fats have a potent anti-rachitic action.
(2) That other footstuffs, more particularly cereals like bread, have a rickets-producing effect.

It is certain that lack of exercise induces the laying on of fat, which is formed partly from the fat eaten, but, to a much greater extent, from the carbohydrates of the food. Whatever its origin the laying on of fat involves the immobility of the anti-rachitic vitamine which is stored with the fat in the connective tissue. Exercise burns up the fat and prevents the excessive conversion of carbohydrate to fat, and therefore gives the body the opportunity of making full use of the vitamine content of the diet.

Another influence of exercise is on the energy-bearing elements of the diet like bread. Other conditions being equal, the greater the amount of bread and other cereals, the more rapidly do the animals grow and put on weight. The greater therefore is the demand on calcium salts and the substances in the body controlling calcification processes. There is, in consequence, a greater laying down of non-calcified bone (osteoid tissue), and rickets results. Exercise hastens the combustion of bread and other energy-bearing substances with a like action, and these substances are afforded less opportunity of participating in the formation of the body tissues.

These two effects of exercise on the metabolism, viz. the prevention of demobilization of the anti-rachitic vitamine in the dépôt fats and the prevention of energy-bearing substances like bread from participating to an inordinate extent in the building up of body tissues, account for, no doubt, some part of its anti-rachitic action. In view, however, of the experimental results obtained with dried thyroid, described below, which also stimulates the metabolism, I am inclined to think that exercise, in inhibiting rickets to some extent, acts also in a way which is not at present understood.

Summary.

Exercise has an anti-rachitic effect in puppies, but this action is not only subsidiary to diet, but even the possibility of exercise is directly dependent on the quality of the diet. It has been shown above

(1) That puppies during absolute confinement will not develop rickets if the diet is good.

(2) That puppies allowed unlimited freedom will develop rickets on the rickets-producing diets used in these experiments.

(3) That rachitic puppies in confinement can be cured by the addition to the diet of whole milk, cod-liver oil, and egg yolk (substances rich in the anti-rachitic vitamine), and more especially if meat is also present in the food.

Reasons are given which indicate that the effect of exercise on rickets in children as compared with puppies is even of less account.

VI. THE EFFECTS OF ADDING THYROIDEUM SICCUM TO RICKET-PRODUCING DIETS

In an earlier publication I suggested that the anti-rachitic effect of exercise might be due to the increase of metabolism that it brings about. This would prevent the conversion of carbohydrate to fat and the deposition of the latter in subcutaneous dépôts. Demobilization of anti-rachitic vitamine would thus be inhibited. Besides ensuring better activity of this vitamine, it would diminish the influence of bread and other energy-bearing material deficient in anti-rachitic vitamine, in so far as the structure of new tissue was concerned.

It was further suggested that the anti-rachitic effect of meat might be to some extent explained by the increase in metabolism that it causes.

If this were the whole explanation of the anti-rachitic effects produced by exercise and meat, it follows that any method of increasing metabolism would have the same action. One of the best methods of increasing the metabolism is by giving thyroid gland to eat. Consequently a few experiments were made to test the effect of thyroid feeding on the development of rickets.

The following experiments show that adding thyroid to a rickets-producing diet has little or no effect on the development of rickets under the conditions described.

Effect of thyroideum siccum.

General Diet.

Exp. 342 and 343 ate

Separated milk 175 c.c.	Lemon juice 5 c.c.
Bread 50–150 grm.	Olive oil 10 c.c.
Yeast 5 grm.	Meat 15–20 grm.
Salt 1 grm.	

Terriers. Age at beginning, 7 weeks.
Outside kennels throughout. No exercise.

In addition 342 received dried thyroid varying between 5 and 30 grains per diem—on most days 10 grains or more. It will be noticed how large were the doses of thyroid given.

The energy of the diets of the two puppies was kept constant for

seven weeks of the experiment, after which period the thyroid dog did not finish up its ration. By this time, however, the results obtained by radiograph made it clear that the thyroid had not prevented rickets.

The radiographs of 342 and 343 after twelve weeks of feeding are seen in Figs. 110 and 111. The weight curves are shown in Fig. 112. It is obvious, since the energy of the diets was the same, and the animals were living under strictly comparable conditions, that the thyroid had increased the oxidation processes of 342, for its increase in weight is much smaller than 343. In spite of this increase in metabolism there was no well-defined anti-rachitic effect present.

Whether thyroid would exhibit an anti-rachitic action if the diet contained a fat with anti-rachitic vitamine such as butter has not been tested. Possibly it would do so, but with olive oil as the sole fat of the diet the effect is apparently not produced. Also when linseed oil was the fat of the diet, thyroid by mouth did not prevent rickets.

Summary.

The increase in metabolism produced by exercise and meat cannot alone explain their anti-rachitic effect, for the addition of thyroid gland to the diet, while increasing the metabolism, did not produce any large anti-rachitic action.

VII. THE HYPOTHESIS THAT RICKETS IS DUE TO AN INFECTION

Among the many causes that have been put forward as explaining the development of rickets, infection finds a place, and even at the present time this hypothesis is viewed with favour by some.

In recent times the work of Morpurgo (35), J. Koch (27), Marfan (28), and Bull (29) has been advanced in favour of the view that rickets has an infective origin.

The results of this extensive research lend no support to this view. Animals have been kept under all possible conditions, both of segregation and close contact, and I have never made any observations that would lead me to believe that the results were being influenced by an extraneous circumstance such as infection. It appears to me to be probable, however, that illness of any kind acts in the direction of producing rickets, so that a border-line case may develop rickets, and slight rickets be made worse if illness, more particularly an illness giving rise to pyrexia, intervenes. I can offer no evidence in support of this statement, which is only an impression produced by observing animals when suffering from distemper and other disorders.

It is possible that the explanation of the action of the illness in these cases is that the animals were generally more closely confined in warm rooms, and even if this were not the case, they spent most of their time lying at the back of their kennels. Apart from this factor, however, there can be but little doubt that calcium meta-

bolism is gravely deranged during pyrexia. Excellent evidence of this is afforded by the appearance of human teeth defects easily observable after eruption in the enamel—bands and pitting appearing in that enamel which was being laid down during the illness. It is probable that the cessation of calcification processes at these times is an indication that calcium is being used elsewhere in assisting the tissues of body to defend themselves against toxic agencies, for there seems no doubt that the addition to a diet of plenty of whole milk containing, among other things, abundant calcium salts and anti-rachitic vitamine, not only has desirable curative effects, but also plays a large part in actually preventing disease. While, however, there is good reason for thinking that an infectious illness interferes with the calcification of bone, and might, therefore, either increase the conditions suitable for the development of rickets or even make the disease worse, it is quite another matter to describe rickets as due to an infection. Rickets is a notoriously ' healthy ' disease, very insidious in nature, and is often found in animals and children which, at first sight, are not only well but fat and flourishing and taking their food with an appetite. It is only later, when the disease is developed, that a distaste for food is seen and the animals begin to lose weight. It is, also, after the appearance of rickets, that catarrhal conditions and great susceptibility to intercurrent infection develops, although, of course, these may be found quite independently of rickets.

It is impossible for me to believe that the drastic treatment of J. Koch (27) to produce rickets in puppies, in which work he injected intravenously cultures of streptococci into the animals, can have any bearing on the disease of rickets in children. In these experiments the animals were made very ill, developed high pyrexia, swollen joints full of fluid, which were very painful, and often made it impossible for the animals to walk for ten to fourteen days, and crippled them for longer periods. Quite apart from the effect of the severe illness, the complete incapability of movement, following the streptococcal injections, would tend to increase rickets unless the animals were well fed. The experimental conditions of J. Koch's work are wholly artificial, and although they might lead to interesting information concerning the effect of illness on calcification processes they do not prove the hypothesis as to the infective origin of rickets.

The experimental results of Morpurgo (35) are more difficult to explain. He obtained rachitic changes in a large proportion of rats as the result of injecting cultures of a diplococcus, previously isolated from laboratory rats among whom a spontaneous outbreak of late rickets had appeared. In these experiments there was a long latent period of 2 to 3 months before there was any evidence of abnormality in the young inoculated rats. Schmorl states that he has produced rickets in two only out of many experimental rats by inoculating them with tissues of rachitic animals. It is necessary to add that but little attention was given to dietetic conditions in any of these experiments on infection.

It seems to me probable that the support given by some clinicians to the infective hypothesis of rickets is due to their mixing up cause and effect. Instead of the catarrhal conditions, that so often develop

in rickety children, being the cause of rickets, both the susceptibility
to catarrh and the rachitic condition are, to my mind, caused by
wrong dieting such as has been described in this paper. It is im-
pressive to observe the difference in susceptibility to diseases like
distemper and mange in puppies which are receiving rickets-producing
and those eating good diets. The same difference in the resistance
and rate of cure is seen when puppies on these diets develop an
intercurrent infection. In fact it has become my practice to kill off
all the puppies as soon as distemper is introduced into the kennels,
because of the experience that the animals on the deficient diets will
probably develop the disease severely.

Summary.

All my experience is against the hypothesis that rickets is due
to an infection, although it is probable that a superadded infective
state interferes with calcification processes of bone, and makes the
conditions more suitable for the development of the disease. The
dietetic conditions suitable for the production of rachitic changes
lowers the resistance of an animal very greatly to infective agencies
of all kinds.

VIII. OTHER DEFECTS WHICH DEVELOP IN PUPPIES EATING RICKETS-PRODUCING DIETS

(a) Susceptibility to Anaesthetics.

The necessity of anaesthetizing animals for radiographic exami-
nation brought out a fact which is of practical importance and
deserves further investigation. No systematic examination of the
point has been made in this work, and I wish here only to record the
fact that dietetic deficiencies introduce dangers into anaesthesia
which do not appear to have been described.

For a few weeks after receiving the rickets-producing diets the
puppies could be anaesthetized with fair safety, and reacted in a
similar way to animals receiving fuller diets. They recovered from
the anaesthesia in the ordinary way and proceeded to eat their diets.
After the experimental conditions had continued from six to ten
weeks, according to their severity, it became dangerous to anaesthet-
ize these puppies. The danger was of two kinds :

(1) Unless great care was used, the animals sometimes died during
anaesthesia of heart failure.

(2) A more common occurrence was that after anaesthesia the
animals never again became normal under the conditions of the
experiment. Either they died within a few days or, more frequently,
went off their food and lost weight and were therefore killed. This
latter state, which was a kind of malaise, often continued for weeks.
If the object of the experiment had been attained, they could usually
be brought back to health by changing the diet to a good one, and
especially by giving them plenty of whole milk.

In anaesthetizing the animals it was customary to inject morphine
(about $\frac{3}{4}$ c.c. of a 1 per cent. solution per kilogram body weight),

and to use a mixture of chloroform and ether (2 to 3). In specially dangerous cases ether alone was used. In later experiments preliminary morphine injections were often omitted, but this did not make much difference to the general results recorded above. Omission of the morphine naturally decreases the danger to respiratory failure, but this is not a great advantage, partly because it is easy to keep a careful look-out for this incident, but also because, if noticed early, recovery usually follows artificial respiration. It is heart failure which is the crux of the matter. It may come on at any time during anaesthesia ; it is not easy to observe, and recovery after its onset is specially difficult to bring about. It seems as if the diets deficient in the anti-rachitic vitamine and rich in bread produce pathological changes in the heart, possibly of the same nature as those changes which develop in the voluntary muscle of rachitic animals, so that it becomes easily knocked out by poisonous substances like anaesthetics.

What the chain of events happens to be in the general illness of the rachitic animals after recovery from anaesthesia, I do not know at the present time, but few puppies which have developed severe rickets, ever recover to the state present before anaesthesia unless the diet is changed.

(b) Nervous Symptoms.

The appearance of nervous symptoms in puppies eating defective diets is common. They can be classified into three main groups :

(1) In animals confined to their kennels, a common occurrence is that on being allowed freedom they are incapable of running straight. Often they run round and round in a small circle. At other times they behave as if intoxicated, starting off for a few steps in one direction, swaying in another direction, and then falling over. This may be repeated again and again until the puppy comes to the conclusion that it cannot arrive at any point it aims at and then it sits down. In both these cases it appears as if there were something wrong in the vestibular nerves or cerebellum.

(2) Paralysis especially of the hind legs. This condition was especially common in the experiments where casein was added to the diets, and sometimes even when the diet contained Fat-soluble A. Nor did recovery take place simply on removal of the casein. One of the most rapid cases of cure followed the removal of acid caseinogen and addition of whey to the diet—in this experiment the animal was eating butter (324). The addition of the ash of separated milk powder also brought about recovery in another animal (325). An abundance of whole milk quickly changes an animal incapable of movement into an active puppy, if the bone deformities allow activity. At all events the paralytic condition disappears. I do not know what pathological changes accompany this paralytic state, i. e. whether they are muscular or nervous. The curative effect of whole milk, whey or milk ash and butter suggests that the defect arises from some abnormality of calcium metabolism.

(3) Tetany and Convulsions. The association of these conditions with rickets is well known, and occasionally they were seen in the rachitic animals. This did not happen as frequently as might be

expected. Here again the addition of casein to a diet deficient in the anti-rachitic vitamine seemed to have a special power for calling forth tetany and convulsions. The addition of egg yolk to the diet of one dog suffering in this way did not bring about recovery, although a cure of the rachitic condition was started.

(c) Keratomalacia and Diminished Resistance to Infection.

A great deal has been written in recent years as to the susceptibility of animals eating defective diets to keratomalacia, and it is now placed among the ' deficiency diseases '. Surprisingly few of my animals developed the condition, but it was seen at different times in puppies eating linseed oil, cotton-seed oil, lard, autoclaved and oxidized butter as fat elements, also in pregnant bitches eating diets deficient in the Fat-soluble vitamine. As has been often observed by other workers in rats, children, and dogs, it cleared up quickly, if caught at an early stage, on the addition of cod-liver oil to the diet. In other untreated cases it rapidly went on to ulceration, suppuration, and blindness.

One case, lard (Exp. 295), cleared up without change of diet. I was impressed by the relation of the type of bedding used in the kennels to the development of the disease. When sawdust was used, the eye disease was more common. With straw and shavings the condition was but rarely found. It is difficult to avoid the conclusion that the irritating action of the sawdust on the eyes was a predisposing factor.

The variation in resistance of the various dogs to distemper, broncho-pneumonia, and mange dependent on the type of diet has already been mentioned.

Summary.

Diets defective in quality but abundant in quantity may be responsible for the following conditions arising in animals :

(1) Heart failure during anaesthesia and difficulty in recovery so that after anaesthesia they refuse food and lose weight.
(2) Several types of nervous defects including inco-ordinated movements, paralysis, convulsions, and tetany.
(3) Keratomalacia.
(4) Increased susceptibility and lowered resistance to distemper and other catarrhal conditions, broncho-pneumonia, and skin affections like mange.

IX. DISCUSSION OF RESULTS

In this work an attempt has been made to examine the influence exerted by the various factors of diet and environment on the production of rickets in puppies, the observations being principally directed to the alterations in the calcification processes of growing bone produced by dietetic and other changes. It has been shown that many of the food elements exert a potent influence on the operation of bone calcification or on growth, or on both, and, moreover, that there is great interplay among these substances. So close, in fact, is this interrelation among the dietetic elements that a condition which

appears of prime importance at one time may sink into relative insignificance at another time. Although numerous experiments have been carried out testing the effect of one variable at a time, so many combinations and permutations are possible that much remains to be done. Until all the variations have been tested there is a danger that important points have been missed and the relative importance of the different effects wrongly evaluated.

The following conditions tend to prevent rickets in puppies :

(1) Plenty of calcium and phosphorus in the diet.
(2) Something associated with certain fats probably identical with the Fat-soluble vitamine.
(3) Meat.
(4) The possibility of exercise.

On the other hand, conditions which inhibit calcification or increase growth relatively to calcification so that defectively calcified bone results are :

(1) A deficiency of calcium and phosphorus in diet.
(2) A deficiency of fat containing the anti-rachitic vitamine in diet.
(3) Excess of bread, other cereals, and carbohydrates.
(4) Absence of meat.
(5) Excess of the protein moiety of caseinogen free from calcium.
(6) Confinement.

Of these conditions, probably the most common cause of rickets in children is a combination of relatively deficient anti-rachitic vitamine and excessive bread. In late and adolescent rickets I think it probable that deficient calcium in the diet is also a causative agent and is possibly the most important defect. It is to be remembered that, wherever there is growth of bone with large defective calcification, many of the clinical indications of rickets will develop.

Because of the inter-dependence of all these dietetic factors it is impossible to say what is the absolute amount of each necessary to produce the optimum results. It is a question of balance, and the greater the number of substances having an anti-rachitic effect that are eaten the less important are the remaining factors for the production of perfect bones.

The most interesting of the actions is the calcification influence exerted by the anti-rachitic vitamine. This action can be emphasized or antagonized by other conditions. If the diet contains a sufficiency of calcium and phosphorus, the presence of meat and the possibility of exercise make a small amount of the anti-rachitic vitamine very effective. On the other hand, excess of bread, causing the animal to put on weight rapidly, combined with confinement or some special condition, such as altering the caseinogen-calcium balance, make the anti-rachitic vitamine less effective. The aiding of and detracting from effectiveness by other dietetic constituents applies not only to the anti-rachitic vitamine but to other elements of diet, so that the so-called law of the minimum is inadequate to explain the problems of nutrition. The minimum of each substance for growth and perfect health varies with the amounts and kinds of other food elements eaten.

Up to the present but little light has been thrown on the problem as to the way in which the anti-rachitic vitamine acts. I have given some evidence that its influence on calcification is of an indirect nature. It is possible that closer examination of the accumulated material will make it possible to get a better insight into the mode of action of this substance. Until this evidence is forthcoming and further experiments are made, it is useless to discuss the action of anti-rachitic vitamine and its possible relation to organs of internal secretion, although the function of controlling calcification has been ascribed at one time or another to all the endocrine glands.

One other element of the diet concerned in calcification I have not discussed in this paper, viz. the anti-scorbutic vitamine. The brittle bones found in scurvy are sufficient evidence of the part played by this vitamine in the calcification of bone. Its absence from the diet appears to be associated with the actual removal of calcium salts from calcified bone, and, when a diet is relatively deficient in both anti-rachitic and anti-scorbutic vitamine, very bad calcification results. I have left this side of the question alone in this publication because of a desire to consider the disease of rickets uncomplicated by the scorbutic condition, and, for the past three years of the research, the diets have contained a constant additional amount of anti-scorbutic vitamine. In the case of children the diseases of rickets and scurvy are no doubt often associated. It is desirable that experiments should be carried out on the anti-scorbutic vitamine and its relation to the other elements of the diet. From observations made during the course of this research I think it probable that the anti-scorbutic vitamine does not hold the position of independence in the diet usually assigned to it.

I am not greatly concerned at present with the multifarious hypotheses as to the aetiology of rickets, for we have first to get definite evidence of the facts of the case. To combine the facts into a simple general hypothesis, at this stage of the work at least, seems impossible except to state that some elements of the diet assist in the calcification of bone (anti-rachitic vitamine), and others inhibit it (protein moiety of caseinogen in milk as prepared by acid precipitation of milk), while some increase growth and allow calcification processes to lag behind (bread and cereals, carbohydrate). The greater the growth the more necessary is it to have in the diet, and absorbed from the alimentary canal, substances which aid in calcifying bone, e. g. calcium, phosphorus, and anti-rachitic vitamine. If these latter substances are relatively deficient or defective in their action rickets will result. In addition to the dietetic elements there is the effect of exercise to be considered. This aids the processes of calcification. But, if a child is correctly fed, the question of exercise appears to me to be negligible, partly because exercise is not so necessary when calcification processes are strongly stimulated by the dietetic elements and partly because an adequately fed child will get exercise in the form of small movements under any conditions. If children are improperly fed, from the point of view of this research, they will almost certainly react, as shown in the case of puppies, by not taking exercise.

Although most of the facts described above will be accepted by

clinicians as applying to children, some points, more particularly as regards the action and distribution of the anti-rachitic vitamine, remain untried. Tests are now being carried out in Vienna by the Medical Research Council, and it will be interesting to see whether the results obtained are in accordance with those described in this paper. For it is upon the child that the final tests must be made, and it lies with the clinician to appraise the results of the experiments on animals described in this work.

APPENDIX

Since this paper was written researches on rickets and calcification processes in bones by McCollum and his co-workers have been published (38). In their work rats have been the experimental animals used and McCollum has confirmed the effect of cod-liver oil in stimulating calcification processes after the production of rickets by defective diets. In a still later paper (39) the production of rickets in rats by a combined deficiency of Fat-Soluble vitamine and phosphorus is described by the same authors.

I have also had the privilege of seeing results obtained by Professor Korenchevsky, working on behalf of the Medical Research Council at the Lister Institute, in which he produces rachitic changes in the bones of rats by diets deficient in both Fat-Soluble vitamine and calcium salts. This unpublished investigation of Professor Korenchewsky seems to confirm and extend many of the facts dealing with vitamines and calcium described above.

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ILLUSTRATIONS

FIGURES 1–129

Fig. 1. Child with rickets.

Fig. 2. Retriever with rickets.

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Fig. 3. Exp. 176. Radiograph after
9 weeks of diet. Linseed oil 10 c.c. and
extra separated milk 175 c.c.

Fig. 4. Exp. 177. Radiograph after
17 weeks of diet. Linseed oil 10 c.c.

Fig. 5. Exp. 178. Radiograph after
9 weeks of diet. Cod-liver oil 5–7·5 c.c

Fig. 6. Exp. 179. Radiograph after
14 weeks of diet. Cod-liver oil 10–15 c.c.

Fig. 7. Exp. 186. Radiograph after
7 weeks of diet. Linseed oil 10 c.c.

Fig. 8. Exp. 187. Radiograph after
7 weeks of diet. Cotton-seed oil 10 c.c.

Fig. 9. Exp. 189. Radiograph after
10 weeks of diet. Pea-nut (arachis) oil
10 c.c.

Fig. 10. Exp. 190. Radiograph after
10 weeks of diet. Cod-liver oil 10 c.c.

Fig. 11. Exp. 180. Radiograph after
18 weeks of diet. Suet 10 grm.

Fig. 12. Exp. 181. Radiograph after
14 weeks of diet. Lard 10 grm.
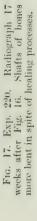
Fig. 13. Exp. 182. Radiograph after
14 weeks of diet. Butter 10 grm.

Fig. 14. Exp. 183. Radiograph after
14 weeks of diet. Babassu oil 10 grm.

Fig. 17. Exp. 220. Radiograph 17 weeks after Fig. 16. Shafts of bones more bent in spite of healing processes.

Fig. 16. Exp. 220. Radiograph 4 weeks after Fig. 15. Diet changed after Fig. 15 to 500 c.c. whole milk instead of 250 c.c. separated milk, palm-kernel oil stopped. Calcification at epiphyses renewed.

Fig. 15. Exp. 220. Radiograph after 9 weeks of diet. (Crushed palm-kernel 10 grm. (much bread eaten). Bad rickets.
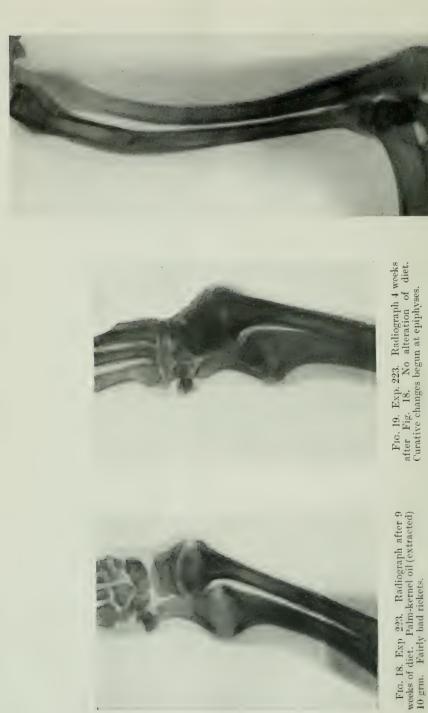
Fig. 20. Exp. 223. Radiograph 21 weeks after Fig. 19. Epiphyseal ends almost normal. Shafts bent and other evidences of abnormality of the bones.

Fig. 19. Exp. 223. Radiograph 4 weeks after Fig. 18. No alteration of diet. Curative changes begun at epiphyses.

Fig. 18. Exp. 223. Radiograph after 9 weeks of diet. Palm-kernel oil (extracted) 10 grm. Fairly bad rickets.

FIG. 21. Exp. 221. Radiograph after 9 weeks of diet. Palm-kernel oil (crushed) 10 grm. Much less bread eaten than 220 (Fig. 15). Slight rickets.

FIG. 22. Exp. 221. Four weeks after Fig. 21. No alteration of diet. Curative changes at epiphyses.
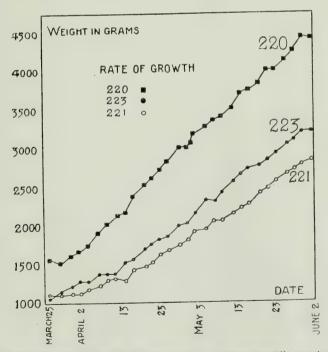
FIG. 23. Weight curves of Exps. 220, 223 and 221. The most rapidly growing puppy, 220 (most bread eaten), developed the worst rickets.

FIG. 24. Exp. 220. Photograph after 20 weeks of rickets-producing followed by curative diet. (See Figs. 15, 16, 17, and 23.)

FIG. 25. Exp. 221. Photograph after 27 weeks of diet. (See Figs. 21, 22, and 23.)

FIG. 26. Exp. 223. Photograph after 27 weeks of diet. (See Figs. 18, 19, 20, and 23.) Rate of growth and amount of rickets intermediate between 220 and 221.
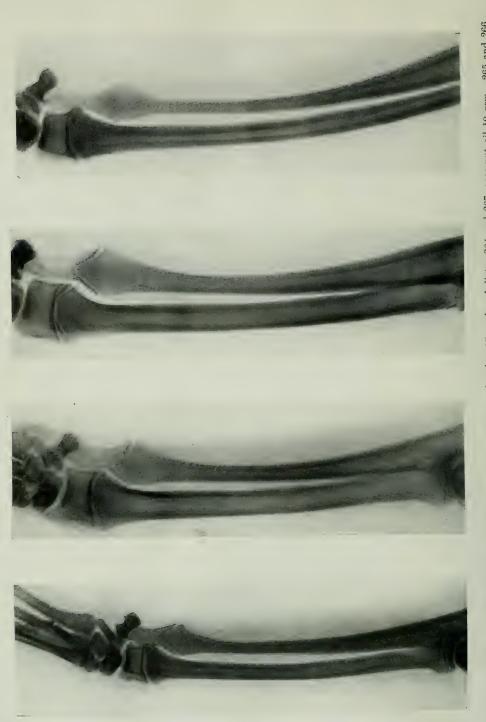
FIG. 27. Exp. 229. Radiograph after 10 weeks of diet. Cod-liver oil 10 c.c.

FIG. 28. Exp. 231. Radiograph after 10 weeks of diet. Cod-liver oil (heated in autoclave to 120° C. for 4 hours) 10 c.c.

FIG. 29. Exp. 232. Radiograph after 10 weeks of diet. Cod-liver oil (heated in autoclave to 120° C. for 2 hours) 10 c.c.

FIGS. 30, 31, 32, and 33. Exps. 264, 265, 266, and 267. Radiographs after 17 weeks of diet. 264 and 267, coco-nut oil 10 grm. 265 and 266, hydrogenated fat 10 grm. Puppies 3–4 months old when diet started. Not of same family. No signs rickets at epiphyses. Note relatively thicker periosteal bone of 264 and 267 (coco-nut) and smaller medullary cavity as compared with 265 and 266 (hydrogenated fat).

Fig. 34. Exp. 282.   Radiograph after
8 weeks of diet.   Lard 10 grm.

Fig. 35. Exp. 283.   Radiograph after
8 weeks of diet.   Suet 10 grm.

Fig. 36. Exp. 284.   Radiograph after
8 weeks of diet.   Bacon fat 10 grm.

Fig. 37. Exp. 285.   Radiograph after
8 weeks of diet.   Pea-nut oil 10 c.c.

Fig. 38. Exp. 328. Radiograph after
19 weeks of diet. Suet 10 grm.

Fig. 39. Exp. 329. Radiograph after
19 weeks of diet. Lard 10 grm.


Fig. 40. Exp. 303. Radiograph after
5 weeks of diet. Cod-liver oil 10 c.c.

Fig. 41. Exp. 304. Radiograph after
5 weeks of diet. Rape-seed oil 10 c.c.

Of the radiographs, Figs. 40–45, olive oil (Fig. 43) shows the worst rickets, lard
(Fig. 44) next. Cod-liver oil (Fig. 40) is normal and the others are intermediate.

Fig. 42. Exp. 305. Radiograph after 5
weeks of diet. Cotton-seed oil 10 c.c.

Fig. 43. Exp. 306. Radiograph after 5
weeks of diet. Olive oil 10 c.c.

Fig. 44. Exp. 307. Radiograph after 5
weeks of diet. Lard 10 grm.

Fig. 45. Exp. 308. Radiograph after 5
weeks of diet. Bacon fat 10 grm.

FIG. 46. Exp. 321. Radiograph after 8
weeks of diet. Autoclaved and oxygenated
butter (120°, 4 hours) 5–10 grm. No
'casein' (acid caseinogen).

FIG. 47. Exp. 322. Radiograph after 8
weeks of diet. Fresh butter 5–10 grm.
Acid caseinogen 10–20 grm.

FIG. 48. Exp. 323. Radiograph after 8 weeks of diet. Autoclaved and oxy-
genated butter (120°, 4 hours) 5–10 grm. and acidic caseinogen (alcohol extracted)
10–20 grm.

Remarks on radiographs 46–50:
Comparison of heated and oxygenated butter with fresh butter, see Figs. 46 and 50.
The heated butter has lost some anti-rachitic action.

Fig. 49. Exp. 324. Radiograph after 8 weeks of diet. Fresh butter 5-10 grm and acidic caseinogen (alcohol extracted) 10-20 grm.

Fig. 50. Exp. 325. Radiograph after 8 weeks of diet. Fresh butter 5-10 grm. No acidic caseinogen.

For action of acidic caseinogen, compare Fig. 48 with Fig. 46, also Figs. 47 and 49 with Fig. 50. The acidic caseinogen has greatly increased the rachitic condition.

For comparison of unextracted acidic caseinogen with alcohol extracted acidic caseinogen, see Figs. 47 and 49. There is but little difference between these radiographs both being bad from the point of view of rickets.

FIG. 51. Exp. 144. Radiograph taken some time after death. Length of experiment 5 months. Rapidly growing puppy, 50 grm. lean meat, 10 c.c. linseed oil. Much bread eaten.

FIG. 52. Exp. 336. Radiograph after 10 weeks of diet. Cod-liver oil 10 c.c.

FIG. 53. Exp. 337. Radiograph after 10 weeks of diet. Cod-liver oil (heated 120° C. 4 hours and oxidized) 10 c.c.

FIG. 54. Exp. 338. Radiograph after 10 weeks of diet. Pea-nut (arachis) oil 10 c.c.

FIG. 55. Exp. 339. Radiograph after 10 weeks of diet. Olive oil 10 c.c.

FIG. 56. Exp. 340. Radiograph after 10 weeks of diet. Coco-nut oil 10 grm.

FIG. 57. Exp. 341. Radiograph after 10 weeks of diet. Cotton-seed oil 10 c.c.
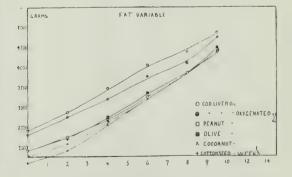
FIG. 58. Weight curves of 336–341. Note parallel rates of growth. All elements of diet quantitatively controlled. Type of fat only varying.

In Exps. 336–341 olive oil (339) had the worst rickets, coco-nut (340) and cotton-seed (341) slight rickets. A month after these radiographs were taken pea-nut (338) had developed some rachitic changes whereas cod-liver (336) and autoclaved cod-liver (337) remained normal throughout the experiment. All these animals were confined.

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Fig. 59. Exp. 172. Radiograph after 13 weeks of diet. 10 grm. butter and 10 c.c linseed oil. Butter has given protection. Compare with Figs. 60 and 61.

Fig. 60. Exp. 174. Radiograph after 13 weeks of diet. 10 grm. lean meat, 10 c.c linseed oil. Rickets—but meat has had some anti-rachitic effect. See Fig. 7.

Fig. 61. Exp. 175. Radiograph after 13 weeks of diet. 50 grm. lean meat, 10 c.c. linseed oil. Rickets but slightly less than 174 (Fig. 60) which received 10 grm. meat.

Fig. 62. Exp. 351. Radiograph after 8 weeks of diet. 20–30 grm. meat, 10 c.c. linseed oil. Complete freedom (special muzzle) in open air during daytime; outside kennel at night.

Fig. 63. Exp. 352. Radiograph after 8 weeks of diet. No meat, 10 c.c. linseed oil. Complete freedom (special muzzle) in open air during daytime; outside kennel at night.

Fig. 64. Exp. 353. Radiograph after 8 weeks of diet. 20–30 grm. meat, 10 c.c. linseed oil. Confined, outside kennel.

Fig. 65. Exp. 354. Radiograph after 8 weeks of diet. No meat, 10 c.c. linseed oil. Confined, outside kennel.
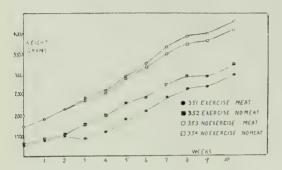
FIG. 66. Weight curves 351, 352, 353, and 354.

FIG. 67. Exp. 299. Radiograph after 13 weeks of diet. Meat protein 20 grm., linseed oil 10 c.c.

FIG. 68. Exp. 300. Radiograph after 13 weeks of diet. Casein (edible, alkaline) 20 grm., linseed oil 10 c.c.

FIG. 69. Exp. 301. Radiograph after 13 weeks of diet. No extra protein, linseed oil 10 c.c. Control to 299 and 300.

Fig. 70. Exp. 299. Radiograph after 18 weeks of diet. Compare Fig. 67. Rickets slight and about the same.

Fig. 71. Exp. 300. Radiograph after 18 weeks of diet. Compare Fig. 68. Rickets slightly improved. Animal off diet.

Fig. 72. Exp. 301. Radiograph after 18 weeks of diet. Compare Fig. 69. Rickets progressed. Now distinctly worse than 299 (Fig. 70).

FIG. 73. Exp. 320.   Radiograph after 15 weeks of diet. 75 grm. bread. Slight rickets.

FIG. 74. Exp. 319.   Radiograph after 15 weeks of diet.   150–200 grm. bread. Fairly bad rickets.
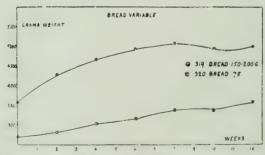
FIG. 75. Weight curves of 319 and 320. (Bread variable experiment.)

Fig. 76. Exp. 333. Radiograph after 15 weeks of diet. Linseed oil 10 c.c., 50 grm. bread. Slight rickets.

Fig. 77. Exp. 334. Radiograph after 15 weeks of diet. Linseed oil 10 c.c., 90–100 grm. bread. Worse rickets than 333 (Fig. 76).

Fig. 78. Exp. 335. Radiograph after 15 weeks of diet. Linseed oil 10 c.c., 150–180 grm. bread. Bad rickets.
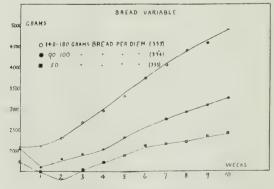
Fig. 79. Weight curves of 333 (Fig. 76), 334 (Fig. 77), and 335 (Fig. 78). (Bread variable experiment.)

Fig. 80. Exp. 322. Radiograph after 2 weeks of altered diet—13 weeks after beginning of experiment. Bread greatly reduced, butter increased to 15 grm. For previous diet see notes Fig. 47.

Fig. 81. Exp. 322. Radiograph 3 weeks after a further alteration in diet. Bread increased to 190 grm., acidic caseinogen replaced by 45 grm. separated milk powder. For previous diets see notes Figs. 80 and 47.

Fig. 82. Exp. 322. Radiograph 5 weeks after Fig. 81. No change of diet. No exercise. Evidence of further improvement in calcification and renewed growth of bone.

Fig. 83. Exp. 324   Radiograph after 2 weeks of altered diet—13 weeks after beginning of experiment.   Bread increased to 190 grm., butter to 15 grm., and acidic caseinogen removed.   For previous diet see notes Fig. 49.

Fig. 84. Exp. 324.   Radiograph 4 weeks after Fig. 83.   Diet unaltered.   Healing processes brought about by removal of acidic caseinogen evident.

Fig. 85. Exp. 324.   Radiograph 5 weeks after further alteration in diet.   Whey from 450 c.c. separated milk added.   For previous diets see notes of Figs. 83 and 49. Healing process quite advanced.   Before addition of whey this animal was paralysed in hind limbs.   No exercise.

Fig. 86. Exp. 325. Radiograph 16 days after altered diet. Thirteen weeks after beginning of experiment. Diet now contains 15 grm. acidic caseinogen, 15 grm. butter, 170 grm. bread. For previous diet see notes of Fig. 50. Rickets has now developed, compare with Fig. 50.

Fig. 87. Exp. 325. Radiograph 4 weeks after Fig. 86. Rickets has further progressed.

Fig. 88. Exp. 325. Radiograph after 5 weeks of a further alteration in diet. Acidic caseinogen removed, bread raised to 190 grm. and the ash of 45 grm. of separated milk powder added. For previous diets see notes of Figs. 86 and 50. Recovery process well started by change of diet. There was also improvement in paretic condition. No exercise.

FIG. 89. Exp. 198. Radiograph after 3 months of a good diet and confinement. Whole milk 250 c.c., meat 20 grm., cod-liver oil 5 c.c. Normal.

FIG. 90. Exp. 198. Photograph of puppy after confinement on a good diet (see notes Fig. 89).

FIG. 91. Exp. 198. Radiograph 15 months after change to defective diet—separated milk, linseed oil, &c. Bones have remained normal. For previous diet see notes of Fig. 89. Outside kennel. Compare with bones of 192 (Fig. 99). Periosteal bone is thick and the marrow cavity small as compared with 192 (Fig. 99).

Fig. 92. Exp. 199. (Brother of 198.) Radiograph after 10 weeks of diet. Linseed oil, &c. Complete freedom with special muzzle during daytime.

Fig. 93. Exp. 199. Radiograph 4 weeks after Fig. 92. No alterations in diet or environment. Recovery processes started at epiphyses.

Fig. 94. Exp. 199. Radiograph 4 weeks after Fig. 93. Conditions unaltered Further recovery at epiphyses (self cure). In spite of recovery of calcification at epiphyses the calcium of the periosteal bone remained low.

Fig. 95. Exp. 193. Radiograph after 17 weeks of diet. Linseed oil, &c. Confined. Bad rickets.

Fig. 96. Exp. 192. (Brother of 193.) Radiograph after 17 weeks of diet. Linseed oil, &c. Exercise. Bad rickets but not quite as bad as 193.

FIG. 97. Exp. 192   Radiograph 7 weeks after alteration to good diet.   Cod-liver oil and meat instead of linseed oil.   On deficient diet puppy became incapable of moving about but made rapid recovery on change of diet.

FIG. 98. Exp. 192.   Radiograph $4\frac{1}{2}$ months after Fig. 97.   Diet unaltered. Further recovery at epiphyses but shafts of bones bent.

FIG. 99. Exp. 192.   Radiograph 6 months after alteration back to defective diet.   Linseed oil in place of cod-liver oil. For previous diets see notes, Figs. 97 and 96.   No evidence of further rickets.   Note thin periosteal bone and thick marrow cavity as compared with Exp. 198, Fig. 91.

FIG. 100. Exp. 250. Radiograph after 9 weeks of diet. Linseed oil 10 c.c., casein 20 grm. (edible, alkaline). Bad rickets.

FIG. 101. Exp. 250. Radiograph 4 weeks after change of diet. Casein removed and 2 egg yolks added. Calcification at epiphyses renewed. Compare with Figs. 103 and 105. No exercise since change of diet.

FIG. 102. Exp. 251. Radiograph after 9 weeks of diet. Linseed oil 10 c.c. No exercise. Bad rickets.

FIG. 103. Exp. 251. Radiograph 4 weeks after change of diet. Two whites of eggs added. Rachitic condition stationary. Compare with Figs. 101 and 105. No exercise.

Fig. 104. Exp. 252. Radiograph after 9 weeks of diet. Linseed oil 10 c.c. Exercise. Rickets but not as advanced as Exp. 251 (Fig. 102).

Fig. 105. Exp. 252. Radiograph 4 weeks after Fig. 104. No change in diet. Rickets more pronounced. No exercise last 4 weeks. Control to 250 and 251.

Fig. 106. Exp. 205. Radiograph after 16 weeks of diet. Linseed oil, &c. Rickets.

Fig. 107. Exp. 205. Radiograph 26 days after Fig. 106. 15 c.c. cod-liver oil substituted for linseed oil. Curative changes have commenced at epiphyses.

Fig. 108. Exp. 213. Radiograph after 13 weeks of diet. Rape-seed oil, &c. Exercise. Rickets.

Fig. 109. Exp. 213. Radiograph $3\frac{1}{2}$ weeks after change of diet, 20 grm. butter. No exercise. Curative changes are obvious.

Fig. 110. Exp. 342. Radiograph after 12 weeks of diet. Olive oil, &c. and 5–20 grains thyroideum siccum.

Fig. 111. Exp. 343. Radiograph after 12 weeks of diet. Olive oil, &c., no thyroideum siccum.
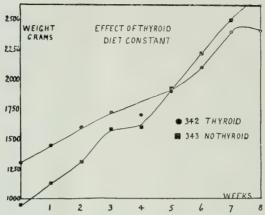
Fig. 112. Weight curves of Exp. 342 and 343 (Figs. 110 and 111). Diets eaten of same energy value. Weight put on by 342 (thyroid) more slowly than 343 (control).

Fig. 113. Exp. 350. Radiograph after 14 weeks of diet and confinement. 'Good' diet. Whole milk 200 c.c., meat 20 grm., dog biscuit 50-150 grm. Quite normal in spite of confinement.

FIG. 114. Microphotograph × 17.   Showing epiphyseal cartilage at lower end
of ulna of a puppy on rickets-producing diet. (Linseed, &c.)

Fig. 115. As 114, but normal owing to 'good' diet. (Suet, &c.)

FIG. 116. Microphotograph × 28. Costochondral junction of rickety puppy (linseed, &c.). Note hypertrophy of proliferating cartilage and irregular invasion of marrow vessels.

Fig. 117. As 116, but of normal puppy on 'good' diet (cod-liver oil, &c.).
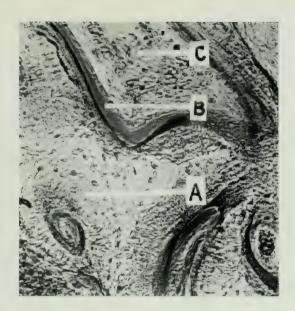
Fig. 118. Microphotograph × 200. Ground section of femur shaft in the region of attachment of muscle. (Undecalcified—Weil's method.) Showing bone (A), osteoid tissue (B), and marrow (C). Rickets-producing diet, but small amount of bread (Exp. 320).
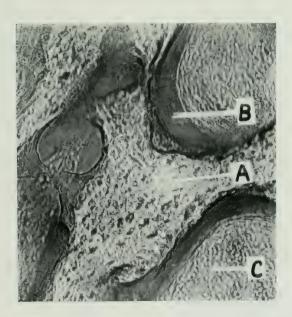
Fig. 119. As 118, but large amount of bread eaten by puppy (Exp. 319). Abundant osteoid tissue (B) evident.
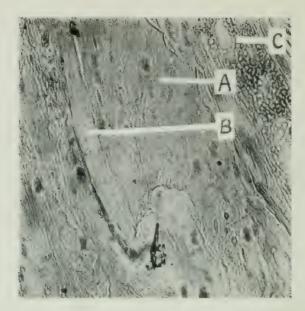
Fig. 120. Microphotograph × 200. Rib partially decalcified by Müller's solution and stained with methylene blue. Rickets-producing diet Bone (A), osteoid tissue (B), marrow (C).
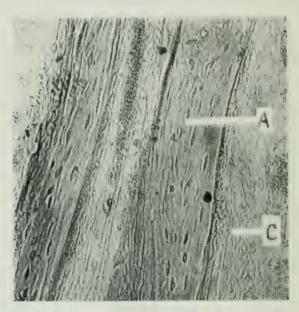
Fig. 121. As 120, but normal bone. Bone (A), marrow (C).
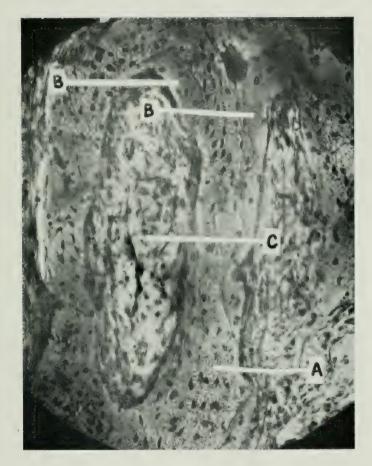
Fig. 122. Microphotograph × 200 of decalcified section of rachitic rib stained by Schmorl's thionin method. Bone (A), osteoid tissue (B), and marrow (C). This method brings out clearly the cells both in the bone and osteoid tissue. Note the comparatively small number of cells with few canaliculi in the osteoid tissue.
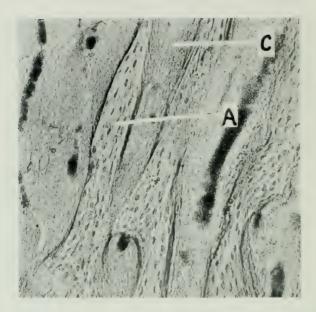
FIG. 123.   Microphotograph × 100 of partially decalcified section of normal rib. Pommer's ammonia carmine method.   Shows bone (A) and marrow (C).

Fig. 124. As 123. but 200 magnification. Rachitic rib. Shows bone (A), osteoid tissue (B) and marrow (C). Fibrillar nature of osteoid tissue brought out.

Fig. 125. Good diet (Exp. 336). No osteoid tissue
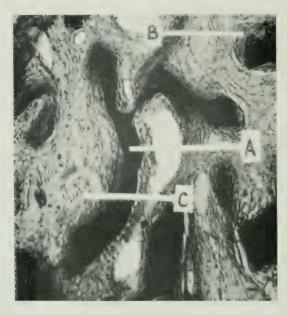
Fig. 126. Linseed oil and little bread (Exp. 333). Some osteoid tissue. Note, magnification slightly higher than Figs. 125 and 127.

FIG. 127. Exp. 335. Linseed oil and large amount of bread. Much osteoid tissue.

FIGS. 125, 126, and 127. Microphotographs of sections of ribs of about the same thickness and from corresponding regions. Sections (undecalcified) cut in gum and stained with silver nitrate and eosin. Calcified bone black. Bone (A), osteoid tissue (B), and marrow (C).
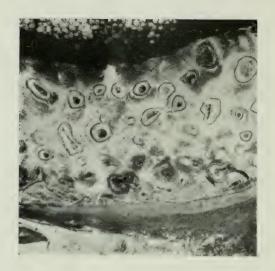
Fig. 128.

Fig. 129.

Figs. 128 and 129 Microphotographs of ground sections (undecalcified) of corre-
sponding parts of the femur shafts of Exp. 303, Fig. 128 (cod-liver oil), and 304,
Fig. 129 (rape-seed oil). Periosteal bone thick and well formed in 303, but thin
and poorly formed in 304

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MEDICAL RESEARCH COUNCIL

no. 62

MEDICAL USES OF RADIUM

Studies of the Effects of Gamma Rays from a large quantity of Radium

by various authors

The Medical Research Council.

INTRODUCTION

In 1919 the Ministry of Munitions, recognizing the assistance which the (then) Medical Research Committee had brought to the Ministry in various directions during the War, offered to deposit with the Committee for the purposes of medical research nearly 5 grammes of hydrated radium bromide—or about $2\frac{1}{2}$ grammes of radium element—during the period between its collection from innumerable gun-sights, watch-dials and other instruments of war, and its final disposal for other purposes. This offer was gratefully accepted, and the whole quantity of radium salt thus made available for research work was, in the first instance, put into the charge of the late Mr. Cecil R. C. Lyster, Professor W. S. Lazarus-Barlow, and Professor Sidney Russ, who, by kind permission of the authorities at the Middlesex Hospital, accepted the responsibility for its safe custody under safeguards approved by the Ministry and the Committee.

The immediate object of the inquiries thus begun was to determine the curative value in malignant disease of penetrating radiation of extremely short wave-length, like that of the *gamma* rays of radium, with a special view to ascertaining whether the use of this very large amount of radium would give appreciably different results, whether in kind or degree, than had been obtained hitherto with quantities of about a tenth of the amount. The work was done in the Cancer Wards and Research Laboratories of the Middlesex Hospital, by courtesy of the Weekly Board, and with the clinical collaboration of the physicians and surgeons. When the radium salt was not in actual use for the treatment of patients, it was employed for the experimental exposure of various animals, and for this side of the work a whole-time research grant was made to Dr. Helen Chambers.

The chief results of this phase of the work are given in the present Report. It contains accounts of the methods employed, of the results of treatment of malignant disease, and of the histological examination of irradiated tissues obtained both from human cases and from animals.

In 1920, H. M. Treasury gave their sanction to the formal transference of this radium salt, at its insured value of £72,500, from the Disposal Board of the Ministry of Munitions to the Medical Research Council, in order to maintain its use for research purposes. Reference may here be made to the further steps which this transference allowed the Medical Research Council to take in the initiation of the second phase of their schemes for the effective use of this radium salt.

At the conclusion of the preliminary period of mass experiment at the Middlesex Hospital, the Council arranged for the distribution of the radium salt among several research centres with a view to an extended and co-ordinated inquiry. These arrangements have of necessity taken long to complete. The selection of suitable centres was made only after a careful consideration of many detailed proposals put forward by different institutions desiring to take part in the scheme. The form in which the radium was to be used was then determined in each case, platinum or other containers were made and suitably filled with the

apportioned fractions of the salt, and every fraction so assigned was accurately remeasured at the National Physical Laboratory after a due period of stabilization. The allocation was completed, however, during 1921, and at nearly every selected centre work is already actively in progress. These centres are at present the following:—in London, the Middlesex Hospital, University College Hospital, King's College Hospital, St. Bartholomew's Hospital, the London Hospital, and the Radium Institute; in the Provinces, the General Hospital, Birmingham; in Wales, the King Edward VII Hospital, Cardiff; and in Scotland, the Royal Infirmary, Aberdeen. The Irish Public Health Council in Dublin, also, were entrusted with a fraction of the salt in 1920, and have organized a local scheme of research. At each centre special attention is being concentrated upon particular forms of malignant disease and their treatment, and from each it is expected that a yearly report will be received. In this way it is hoped that the collection of trustworthy information may be greatly accelerated with a view to determining the value of radium treatment in various types of malignant disease in different organs, and the best methods for its application where its value can be established.

The Council have recently appointed a special Committee to advise them upon radiological subjects, and to supervise the practical working of the scheme of radium distribution just described. The members of this Committee are Sir Cuthbert Wallace, K.C.M.G., Sir Humphry Rolleston, K.C.B., Professor S. G. Shattock, F.R.S., Dr. C. Thurstan Holland, Dr. Robert Knox and Professor Sidney Russ. The work of this central advisory body will be supplementary to that of the local research committees and working teams established at the different centres to which radium has been allotted.

The Council are heavily indebted to Professor Sidney Russ for his advice and assistance in many technical questions arising in the manipulations of the radium salt. He has given much time and labour to the designing of the special apparatus needed for the use and custody of the material, and for the protection of the workers from the personal risks which the use of radium involves.

The Council cannot leave unnoticed here the untimely death of Mr. Cecil Lyster, C.B.E., in January 1920. He took a prominent part in the early stages of the work upon which his colleagues now present their Report. His services to the Council in this, and in other ways, valuable as they were, were only a very small part of his devoted and unselfish services to the advancement of medicine, especially in his chosen field of radiology. His own early and pioneer work exposed him to great personal danger because of its nature and its novelty; to this, in fact, he made the sacrifice of his life, after a period of long strain during the war, in which he sought, and most bravely sustained, very heavy additional burdens regardless of any but national and scientific interests.

Medical Research Council,
  15, Buckingham Street,
    London, W. C. 2.   *January 15, 1922.*

MEDICAL USES OF RADIUM

STUDIES OF THE EFFECTS OF GAMMA RAYS FROM A LARGE QUANTITY[1] OF RADIUM

CONTENTS

[1] In the following pages wherever the expression Q dose occurs, it refers to the special radium conditions of this investigation.

1. ON THE USE OF THE GAMMA RAYS FROM A LARGE QUANTITY OF RADIUM IN THE TREATMENT OF MALIGNANT DISEASE

PART I

By SIDNEY RUSS, D.Sc.

(*Joel Professor of Physics, The Middlesex Hospital*).

CONSIDERATIONS OF TECHNIQUE.

At the outset it was decided to restrict ourselves to the external application of the radium and to deal with the gamma rays only. The radium, in the form of bromide, was handed to us in eighteen small glass tubes; these were placed in silver tubes which were set in grooves in the base of a circular brass box of diameter 11·7 cm. and depth 1·7 cm. This box was fitted into another brass box lined with lead, 3 mm. thick on the front and sides, and 20 mm. thick on the back. Any radiation reaching the patient had first to penetrate 3 mm. of lead and about 1 mm. of brass; this latter being the thickness of the lid of the outer brass box; it may therefore be said that we were using only the gamma rays.

It was realized that those who had to deal with the actual application of the radium to the patients would suffer damage from the rays unless special precautions were taken for their safety. The first precaution was to arrange that it should not be necessary to touch the radium box. This was done as follows; the back of the box was fitted with a conical extension, the centre of which was hollowed out so as to receive a split cone situated at one end of a detachable rod four feet long. The split cone could be expanded by a small lever fitted into the handle end of the rod. When this was done the radium box could be carried about firmly attached to one end of the rod; by a movement of the lever it could be released as desired. For general security the radium was kept in a Chubb's safe when not in use; for the protection of people in the building, and of electrical instruments in adjoining rooms from the gamma rays, a lead block with a cavity in it just large enough for the radium box was cast; this lead block (vide fig. 1) weighing 1½ tons, was put inside the safe, and access to the radium was obtained by swinging open a lead door, in design like a breech block. The long arm was then inserted, the conical clutch engaged in the back of the box, and the radium immediately on withdrawal slipped into a small trolley for conveyance by lift to the special ward. This trolley was provided with a lead top two inches thick to protect the person who effected this transfer. Most of these protective appliances were manufactured for us by Messrs. Watson.

The weight of the radium box was 10 lb., which meant, that though held as near as possible to the patient, it could not actually rest upon any part of the body. For horizontal projection the arrangement in Fig. 2 was used, which allowed the radium to be moved along to any desired position.

More often the exposures were required with a vertical projection or inclined thereto at a small angle; to meet this requirement, either a vertical stand with a projecting arm, or a table which could straddle across the patient's bed, was used. With the latter arrangement a hollow wooden cylinder, large enough to hold the radium box, was suspended by an overhead arrangement, and movements of this cylinder at any angle were obtained by a ball and socket joint. By this means it was possible to get the front of the radium box to within a few mm. of the surface irradiated without actual contact.

EXPERIMENTAL BASIS FOR THERAPEUTIC WORK.

The applicator as described had an average gamma ray intensity of 45·6 mgm. per square cm., slightly stronger at the centre than at the periphery. Previous observations with smaller applicators had shown that with an intensity of 22·5 mgm. per sq. cm., an exposure of the skin lasting 7 or 8 hours caused blistering and epilation. A further consideration was that this exposure caused the disappearance of surface carcinomatous nodules in the human subject, and was about the lethal dose for a rapidly growing sarcoma of the rat.

It was decided before making any therapeutic applications to transfer this basis of reference, which had served as a guide to us in other work, to the large radium capsule itself. Rat tumours were exposed in Petri dishes to the gamma radiation, and afterwards inoculated into susceptible rats in order to find the time required for a lethal effect upon the tumour cells. Tumour-bearing rats were also exposed for a number of hours to the radiation and observations made upon the subsequent growth or otherwise of the tumour.

Experiments with Jensen's Rat Sarcoma showed that an exposure of approximately 8 hours to the radium capsule is necessary to ensure that the cells do not grow when subsequently inoculated into normal animals. It was also known that the exposure of these malignant cells to radiation for shorter time than that required to kill them, results in a temporarily delayed rate of growth of the tumour cells with subsequent recovery to their original rate of division. The work of various experimenters has demonstrated that the dose of radiation required to destroy the cells from several strains of malignant tumours in animals is fairly constant. In human malignant disease the dose necessary to cause the tumour cells to be absorbed is known for certain types of growth, particularly for rodent ulcers, and in the case of a malignant breast tumour; this dose was determined for secondary nodules in the skin, and was found to be very similar to that for the animal tumours mentioned.

The general trend of our experiments was to show that an exposure of 4–5 hours would probably be the limits of toleration of the skin to the radiation, and that such an exposure, though not likely in the majority of tumours to be lethal, would have a direct effect in retarding and possibly overcoming growth.

It was quite certain that, in order that the treatment might be satisfactory, a large proportion of the cases would require the irradiation to be effective at a considerable depth below the surface. The fall in intensity of the rays is due partly to the increase in distance from the source and partly to the absorption of the gamma rays by successive layers of tissue. This variation of intensity was found experimentally, and the mode and duration of exposure of the patients were determined after a general consideration of these intensity variations. Where possible several ports of entry for the radiation were selected, but owing to the much greater penetrating power of gamma rays than even 'very hard' X-rays it is often impossible to screen neighbouring tissues from the effects of the gamma rays which are being used.

Some idea of the variation in intensity of the rays as the distance from the surface of the capsule was increased, may be obtained from the data in Table I.

TABLE I.

Distance in cm. from applicator.	Intensity.
0	100
1	90
2	81
3	72
4	63·5
5	56·5
8	33
10	22
15	13

Two additional indicators of the intensity of the radiation were used as guides in the dose to be administered therapeutically. It had been found that rats exposed to a small measured dose of X-rays show a 50 per cent. drop in the number of circulating lymphocytes; for a definite dose of X-rays this is a remarkably constant finding. Rats were therefore subjected to the radium for a time calculated to give the same radiation dose as in the measured dose of X-rays; the subsequent blood changes produced were similar in the two cases. Again, photographic plates were exposed to the gamma radiation, one part of the plate remaining unexposed; on this portion beta rays of known intensity were allowed to act for a time which had a definite basis of reference as regards biological action; in this case a comparison of the beta and gamma ray tints produced on the same photographic plate led to a very similar finding as the observations upon tumour cells; this confirmed our belief that we could not safely exceed a 4–5 hours' exposure over any one surface of the body without producing some damage to the skin.

In measuring the superficial dose of X-rays in therapeutic work extensive use is made of Sabouraud's pastilles; these pastilles are more sensitive to 'soft' than to 'hard' X-rays and in view of the very short wave-length of the gamma rays we were using, it was not anticipated that these pastilles could serve as surface indicators of gamma intensity. This anticipation

proved to be correct; two pastilles exposed flush to the radium box for 16 hours suffered no discoloration at all except at their edges, yet as will be seen later the exposure of patients for about 4 hours, in the majority of cases, resulted in complete loss of hair over the region irradiated.

PART II

By W. S. Lazarus-Barlow, M.D., F.R.C.P., S. Russ, D.Sc., and Helen Chambers, C.B.E., M.D.

(*From the Middlesex Hospital*).

Clinical Treatment.

(The clinical notes recorded are produced with the permission of Mr. Kellock, Mr. Sampson Handley and Mr. Webb who had charge of the patients while in the hospital.)

The use of the applicator containing 4·919 grammes of radium bromide for the treatment of patients with malignant disease was begun in October 1919. The radium has since been in constant use and, during the period from October 1919 to April 1921, 168 cases have been under treatment. The nature of the diseases from which the patients were suffering is shown in Table II (p 13).

In many cases the disease was very advanced when the treatment was begun, and with few exceptions all the patients were surgically inoperable; the high death rate is thus explained. Owing to the extent of the disease it has frequently not been possible to treat the whole region involved. notwithstanding, many of the cases have been temporarily much improved, and the clinical progress has often been of great value as an indication of the local reaction of malignant cells to irradiation.

The results obtained from the use of this large quantity of radium are of special interest because it has been the first opportunity for using such a large source of radiation for deep therapy, and more particularly because it is known that, if penetrating gamma radiation from radium is applied to the surface of the body, under the conditions we have employed, the tissues at a depth of 6 cm. will receive a larger proportional dose of radiation than they would from the application of the most penetrating type of X-radiation at the present time available, the surface intensities being the same in each case.

In a considerable number of the cases under treatment the growths have been near the surface and have come well within this range of 6 cm., and we ought therefore to be in a position, as as far as the limited clinical experience permits, to determine the value of this type of radiation as an agent for destroying malignant cells and, indirectly, the value of deep radiation therapy.

From the preliminary experimental investigation it seemed very probable that, if the treatment with the radium capsule was to be effective the exposures would need to be about 8 hours.

Except in one case of round-celled sarcoma, a type of growth which is generally considered to be specially vulnerable to radiation, the clinical results so far obtained confirm this impression. They indicate that the dose of radiation required to produce a lethal effect on malignant cells, and particularly on carcinoma cells at a depth of a few centimetres from the surface, is a very heavy dose which exceeds an exposure that causes damage to the overlying skin if applied as a single dose from one aspect. When the use of the radium capsule for the treatment of patients was first begun it was felt that injury to the skin was of minor importance, especially in situations where it could, if necessary, be removed, compared with the prospect of being able to destroy the growth cells, and the exposures were in a few cases prolonged to 6 hours. After an interval of two or three weeks these patients developed very severe local dermatitis at the site of irradiation, though in most of the cases the skin was not permanently damaged, and in 3 to 5 weeks had healed. The extent of the damage was found to vary considerably with the local conditions (see also page 18) but in all these cases it was so severe that it was not desirable to prolong the exposures to this extent unless the growth could be effectively treated by such drastic measures. In a few cases treated for superficial recurrences on the chest wall, after radical operations for breast carcinoma, exposures to the radium capsule for 4–5 hours applied as close to the patient as possible has resulted in the complete disappearance of the nodules.

When treating deeper growths such as cases of inoperable breast cancer the capsule has been applied from two and sometimes three aspects. This has been done to avoid too severe damage to the skin, and also in the hope that the breast tumour would receive radiation from each application and thus be treated more effectively than by one exposure. In this way some of the cases have received from 9 to 10 hours' treatment.

The temporary effect has often been very marked, the superficial nodules have disappeared, the whole tumour has become smaller, more movable and less tense and, after an interval of 4 to 8 weeks, 12 of the patients were considered surgically operable, although, when the radiation began, the disease was thought to be too extensive for surgical treatment. Three of these patients were too old for operation to be undertaken ; treatment has been continued and, in all of them, the disease is apparently quiescent. The remaining nine have had the growth removed.

The subsequent history of some of these patients shows that if a breast carcinoma occurs in a well-nourished woman, and the malignant cells infiltrating the pectoral fascia are at a considerable depth from the surface, a total exposure to the radium capsule for 9 hours from two or three aspects is not effective in treating the deeper cells of the growth. although this treatment generally causes severe vesication of the skin. Three cases have recurred at the site of irradiation, and in one patient, after the breast was removed, the pectoral fascia was found scattered with nodules of actively growing tumour.

All the patients in whom the disease has become quiescent were poorly nourished, the growths were in consequence near the surface of the body and the treatment has been repeated ; the malignant cells have thus been subjected to a very heavy dose of radiation.

Notwithstanding some disappointing results, the great temporary improvement obtained in some of the cases of inoperable breast cancer gives reason for thinking that, with the more accessible tumours and with improved methods of technique ; particularly if surgical treatment is combined with the use of buried radium and penetrating radiation from the surface, better results will be assured. And our work is, at present, proceeding on these lines.

That the radiation can be of great value as an adjunct to surgery is illustrated by the following cases :

Case 1. M. A. H., a woman of 50 years of age, had an inoperable fixed carcinoma of the left breast of 8 years' duration. Three radium tubes were inserted into the growth in January 1920, and she was afterwards treated with a five-hour exposure to the radium capsule. In May 1920, the exposure to the radium was repeated for a further period of five hours, and a radical operation for removal of the breast was done in July 1920. The report on the specimen removed stated that the growth had obviously extended beyond the limits of the operation incisions. In January 1921, radium tubes were inserted into enlarged glands in the left supra-clavicular triangle, and this was followed in February by an exposure to the large Q radium for three and a half hours in this region. This patient when last seen in June 1921, 18 months after starting treatment as an inoperable case, is in good general health and doing her ordinary work ; she has no recurrence on the chest wall, and there is no active disease detectable.

Case 2. C. W., a man 69 years of age, was admitted into hospital with a large fungating carcinoma on the calf of the left leg. It had been growing rapidly for six months and measured 11 cm. by 11 cm. in its longest diameters, and projected 3 cm. from the surface level.

Microscopically the growth had a structure resembling a rodent ulcer.

In July 1920 the large Q radium was applied as near as possible to the growth for five hours.

A fortnight later the whole mass had shrunk considerably, and now measured 8 cm. by 8 cm. in the same diameters as before. The most noticeable effect was a very marked decrease in thickness ; this was now only 1 cm.

In July the glands in the groin were removed, and in August 1920 the growth was excised locally and the wound skin-grafted a few days later.

This patient, ten months afterwards, is very well and has no recurrence.

Case 3. E. S., a woman aged 56, had a congenital wart on the front of her knee frequently subject to injury. For eight months it had grown rapidly, and, on admission, there was a fungating malignant growth measuring 12 cm. by 9 cm. in longest diameters and projecting 3·5 cm. from the surface.

In November 1920 the large Q radium was applied as near to the growth as possible for $4\frac{3}{4}$ hours, and, some days later, radium tubes were inserted into the right groin, where there were small enlarged glands.

The growth shrank considerably, though not as much as in the previous case, and in December 1920 it was removed locally, the wound skin-grafted, and the left inguinal glands were excised.

On microscopic examination the growth was found to be a squamous-celled carcinoma.

This patient left the hospital in March 1921. The leg ulcer had healed completely, and the mass of indurated glands in the right groin was smaller than it had been some weeks before.

Under ordinary conditions, had the radium not been available, both of the last two patients would have required amputation.

The effective treatment of malignant tumours is largely a question of applying a dose of radiation of such intensity that it will be lethal to the malignant cells and include the whole of the region involved ; this is shown by the following cases :

Case 4. A man of 56 years of age developed an epithelioma of the lower lip and was operated on in 1916 ; it recurred locally, and, in 1917, it was again removed after the application of radium tubes. In 1920 he was admitted into hospital with a recurrence in the right parotid lymph gland forming a hard, fixed mass 5 cm. by 5 cm. in diameter and 3 cm. in thickness. The skin was not ulcerated, and there was no local recurrence at the primary site.

At this time it was appreciated that the application of the large Q radium alone to cases of epithelioma of the tongue and neck was not successful in doses which had been, until then, employed, and it was decided to increase the dose of radiation by combining its application with the insertion of radium tubes.

In October 1920 three radium tubes of the total value of 96 mgm. were inserted into the growth and were left *in situ* for 24 hours. Ten days later the radium capsule was applied to the surface for six hours. The patient developed, as was expected, a very severe local dermatitis over the area radiated. This recovered after some weeks without having caused ulceration of the skin, and the mass of growth has since entirely disappeared. Six months later there is no recurrence.

Case 5. A. F., a man of 25, had suffered since 1914 from a sarcoma of the left knee arising in the tendon sheaths near the popliteal space. It had been removed surgically four times and had each time recurred. After the second operation in 1917, when the malignant nature of the growth was first recognized, a course of X-ray treatment was begun and he had fortnightly exposures from a Coolidge tube for the next year. In January 1919 the growth had recurred, and radium tubes were inserted and the mass afterwards excised. It recurred again in February 1920, and radium tubes were inserted again in July and October 1920. In November 1920 the growth was excised and it was found that, in the situations where the radium tubes had been inserted, the tissue was largely fibrotic ; in the deeper parts, however, the tubes had not penetrated far enough and the growth had the microscopic structure of a rapidly growing spindle-celled sarcoma, and could not have been completely removed. It was decided to apply the large Q radium from three aspects, so as to ensure that the tissues in the popliteal space received radiation from each application. On November 10, 11, and 12 the radium was applied as near as possible to the surface of the limb for three hours from the back and each side, a total exposure of nine hours being given.

In this case the situation of the disease was such that radium therapy could be applied with some prospect of an effective dose reaching the region involved ; this evidently had not occurred with the previous irradiation. As this was only 7 months ago, it is not long enough to draw definite conclusions as to the ultimate success of the treatment. At the present time the man is doing his ordinary work, leading an active life, and has no obvious recurrence.

Case 6. E. M., a man aged 39, was first seen in December 1920, when he was suffering from a growth in the neck of eight months' duration. There was a fixed mass 7 cm. by 7 cm. in diameter in the left submaxillary region which had recurred after two operations for removal. When first seen he had very severe pain in his neck, and this was soon followed by paralysis of the left facial and spinal accessory nerves due to extension of the growth.

Microscopically the tumour was stated to be a round-celled sarcoma.

The treatment applied consisted of four applications of the radium capsule for periods of 3 to 4 hours to both sides of the neck. Subsequently a gland appeared in one groin and was given radiation.

The growth in the neck rapidly diminished in size after treatment. At the present time, six months later, he is in excellent general health, doing his ordinary work, there is no growth detectable in the neck, and the paralysed nerves have nearly recovered.

OBSERVATIONS UPON THE BLOOD.

Blood counts were made upon the first 36 patients treated with a view to seeing whether blood examinations would be a useful indicator as to the general effect of the radiation exposures.

In some cases after a prolonged treatment there has occurred a definite reduction in the percentage of haemoglobin ; when combined with a pronounced diminution in the lymphocytes, this has served as a warning that the treatment should be suspended for some time.

The first blood count was made just before treatment, a second one 2 days later and, when possible, a third one after 7 days.

The general effect of the radiation was to lower the number of lymphocytes, the action upon the other types of blood-cells being less evident. The extent of this lymphocytic reduction varied very largely as may be seen in Table III. We do not know the reasons for this variation, but in general it appears that larger changes occur when the radiation is applied to the chest and abdomen than when restricted to other parts.

The information obtained from a detailed examination of the blood counts enumerated below, is not of a definite character. No doubt the results are often affected by the condition of sepsis which is such a frequent association of malignant growths.

Table II.

Disease.	No. of cases treated.	Apparently recovered. No growth detectable.	Operation considered inadvisable. Subsequently carried out.	Improved. Disease quiescent.	Disease progressing.	Died.
Sarcoma.						
Neck	8	1	..	..	1	6
Ileum	2	..	..	1	..	1
Shoulder	2	..	..	..	..	2
Femur	2	2				
Fibula	1	..	..	1		
Mediastinum	4	..	..	1	..	3
Upper Jaw	4	..	..	..	1	3
Parotid	3	..	..	..	..	3
Thyroid	1	..	..	..	..	1
Tonsil	1	..	..	..	..	1
Prostate	1	..	..	..	..	1
Abdomen	1	..	..	..	..	1
Orbit	1	..	..	..	..	1
Testis	1	1				
Melanotic Sarcoma	1	..	..	..	..	1
Carcinoma of Breast.						
(a) Operable cases	6	4	..	..	..	2
(b) Inoperable cases	36	..	12	5	10	9
(c) Recurrence after operation	36	3	..	12	8	13
Carcinoma.						
Stomach and Intestines	5	..	..	..	1	4
Rectum	7	..	..	..	..	7
Cervix	2	..	..	..	..	2
Epithelioma.						
Tongue and floor of mouth	28	1	..	2	2	23
Lip	4	1	..	1	..	2
Cheek	1	..	..	..	1	
Pharynx and oesophagus	2	..	..	..	..	2
Palate	1	..	..	..	..	1
Leg	2	2				
Vulva	1	1				
Scrotum	1	..	..	..	1	
Pinna	1	..	..	1		
Rodent Ulcer.	2	..	..	..	.	2

Table III.

Blood counts upon patients exposed to large Q radium

L. = Lymphocytes. P. = Polynuclears. L.M. = Large Mononuclears.
E. = Eosinophils. R.B.C. = Red Blood Count. H. = Haemoglobin.

No. of patient	Site irradiated.		Initial count per c.mm.	Count 2 days after treatment.	Count 7 days after treatment
1	Abdomen. Malignant Colon.	L.	4,030	..	690
		P.	8,450	..	5,480
		L.M.	460	..	440
		E.	60	..	..
		R B C.	5,400,000	..	5,500,000
		H.	100%	..	100%
2	Chest. Recurrent Carcinoma of Breast. (Not ulcerated.)	L.	2,880	970	720
		P.	9,300	7,480	6,400
		L.M.	850	310	880
		E.	70	40	..
		R.B.C.	5,800,000	5,700,000	5,300,000
		H.	96%	96%	92%
3	Chest. Lympho - Sarcoma. (Not ulcerated.) 1st dose.	L.	3,960	890	1,810
		P.	14,230	12,220	7,150
		L.M.	540	1,640	740
		E.	270	150	50
		R.B.C.	5,800,000	5,700,000	6,000,000
		H.	70%	90%	92%
3 (cont.)	2nd dose.	L.	2,780	1,280	2,330
		P.	10,630	12,900	8,270
		L.M.	280	680	440
		E.	210	150	60
		R.B.C.	6,000,000	5,700,000	5,700,000
		H.	100%	96%	96%
4	Neck. Epithelioma of Tongue. Secondary Glands.	L.	6,600	2,200	8,750
		P.	32,200	21,840	23,980
		L.M.	800	240	1,750
		E.	400	120	520
		R.B.C.	4,800,000	4,200,000	3,800,000
		H.	84%	78%	66%
5	Chest. Carcinoma of Breast. (Ulcerated Secondary Glands. 1st dose.	L.	7,660	4,860	2,970
		P.	7,660	6,060	7,280
		L.M.	1,910	900	900
		E.	170	60	60
		R.B.C.	5,200,000	5,300,000	5,300,000
		H.	78%	80%	86%
5 (cont.)	2nd dose.	L.	4,400	3,470	2,260
		P	8,310	6,660	8,030
		L.M.	1,280	820	830
		E.	70	50	60
		R.B.C.	5,200,000	5,400,000	5,200,000
		H.	86%	88%	86%
6	Rectum. Carcinoma of Rectum.	L.	5,100	1,920	2,970
		P.	11,970	9,600	7,480
		L.M.	260	360	440
		E.	260	60	110
		R.B.C.	5,000,000	4,100,000	4,500,000
		H.	64%	50%	46%
7	Neck. Epithelioma of Tongue. Secondary Glands.	L.	6,280	3,800	2,650
		P.	11,380	10,790	6,960
		L.M.	360	460	150
		E.	180	150	50
		R.B.C.	6,100,000	6,100,000	5,200,000
		H.	98%	100%	96%

No. of patient	Site irradiated.		Initial count per c.mm.	Count 2 days after treatment.	Count 7 days after treatment.
8	Abdomen. Sarcoma of Testis.	L.	6,120	2,750	..
		P.	6,850	6.830	..
		L.M.	130	460	..
		E.	200	150	..
		R.B.C.	5,000,000	5,000,000	..
		H.	90%	76%	..
9	Face. Epithelioma of Palate.	L.	4,360	..	2,160 (14 days)
		P.	24,120	..	11,220
		L M.	3,520	..	450
		E.	..	..	80
		R.B.C.	4,800,000	..	4,100,000
		H.	102%	..	88%
10	Rectum. Carcinoma of Rectum.	L.	3,610	1,810	1,790
		P.	6,280	7,220	4,820
		L.M.	310	290	660
		E.	100	190	40
		R.B.C.	5,200,000	5,200,000	4,800,000
		H.	90%	82%	92%
11	Rectum. Carcinoma of Rectum.	L.	6,400	3,250	4,980
		P.	12,900	8,660	5,430
		L.M.	500	470	780
		E.	200	220	
		R.B.C.	4,600,000	4,400,000	5,500,000
		H.	70%	70%	72%
12	Neck. Sarcoma of Neck. (Not ulcerated.)	L.	3,170	1,820	2,290
		P.	5,760	5,690	5,900
		L.M.	190	280	400
		E.	480	120	220
		R.B C.	5,500,000	5,400,000	5,500,000
		H.	94%	96%	90%
13	Chest. Recurrent Carcinoma of Breast. (Not ulcerated.)	L.	2,710	1,602	1,700
		P.	6,030	6.810	4,130
		L.M.	460	310	580
		E.	..	180	
		R.B C.	5,300,000	5.200,000	5,000,000
		H.	80%	78%	64%
14	Chest. Carcinoma of Breast. (Not ulcerated.)	L.	2,590	1,560	..
		P.	4,430	3,020	..
		L.M.	70	70	..
		E.	110	120	..
		R.B.C.	4,600,000	4,800,000	..
		H.	92%	88%	..
15	Chest. Carcinoma of Breast. (Not ulcerated.)	L.	3,190	..	1,980 (14 days)
		P.	4,220	..	4,100
		L.M.	110	..	160
		E.	80	..	60
		R.B.C.	5,400,000	..	5,300,000
		H.	94%	..	90%
16	Chest. Carcinoma of Breast. (Ulcerated.)	L.	2,680	1,730	3,670
		P.	8 540	8,750	10,370
		L.M.	850	270	360
		E.	60	50	..
		R.B.C.	6,400,000	6,200,000	6,400,000
		H.	100%	96%	92%
17	Face Growth of Parotid Region.	L.	2,960	1,980	4,000
		P.	11,400	11,020	9,440
		L.M.	220	130	2,400
		E.	220	70	160
		R.B.C.	5,200,000	4,800,000	5,000,000
		H.	100%	96%	86%

No. of patient.	Site irradiated.		Initial count per c.mm.	Count 2 days after treatment.	Count 7 days after treatment.
18	Chest. Recurrent Carcinoma of Breast. (Ulcerated.)	L. P. L.M. E. R.B.C. H.	2,390 6,350 370 90 5,000,000 88%	2,020 8,400 380 110 5,000,000 90%	1,600 8,150 200 50 4,500,000 74%
19	Chest. Carcinoma of Breast. (Not ulcerated.)	L. P. L.M. E. R.B.C. H.	2,880 6,240 190 290 5,000,000 72%	2,180 6,060 170 .. 5,200,000 72%	.. ..
20	Lower Lip. Epithelioma of Lower Lip.	L. P. L.M. E. R.B.C. H.	3,180 11,100 440 70 5,400,000 54%	3,720 22,080 800 .. 4,900,000 54%	2,280 19,920 1,680 120 5,400,000 54%
21	Bladder. Carcinoma of Bladder.	L. P. L.M. E. R.B.C. H.	2,340 25,110 1,610 150 4,400,000 70%	1,890 36,420 1,390 100 4,600,000 72%	1,790 25,320 410 70 4,000,000 64%
22	Face. Recurrent Glands. Carcinoma of Tongue. (Not ulcerated.)	L. P. L.M. E. R.B.C. H.	3,540 11,990 570 .. 4,600,000 100%	5,280 9,760 800 160 5,100,000 103%	2,770 4,640 310 80 5,400,000 96%
23	Neck. Sarcoma of Neck. (Septic.)	L. P. L.M E. R.B.C. H.	3,340 24,510 1,160 .. 5,300,000 94%	2,660 28,010 470 160 5,600,000 94%	2,880 14,780 1,060 380 5,100,000 90%
24	Rectum. Carcinoma of Lower Rectum.	L. P. L.M. E. R.B.C. H.	3,330 7,570 400 .. 5,500,000 82%	.. ..	2,680 8,660 550 310 5,600,000 82%
25	Face. Epithelioma of Cheek.	L. P. L.M. E. R.B.C. H.	2,300 5,820 260 130 4,800,000 88%	.. ..	1,850 6,600 260 90 4,800,000 86%
26	Neck. Lympho-Sarcoma of Tonsil.	L. P. L.M. E. R.B.C. H.	3,480 18,440 1,160 120 4,400,000 88%	2,910 18,590 780 110 4,600,000 86%	5,380 18,560 1,280 380 4,600,000 86%
27	Thigh. Sarcoma of Femur.	L. P. L.M. E. R.B.C. H.	5,870 3,880 410 50 4,200,000 82%	6,160 4,570 220 60 3,600,000 78%	5,540 3,870 390 .. 4,500,000 84%

No. of patient.	Site irradiated.		Initial count per c.mm.	Count 2 days after treatment.	Count 7 days after treatment.
28	Jaw.	L.	2,660	2,080	2,190
	Epithelioma of	P.	11,540	10,340	10,240
	Tongue.	L.M.	440	520	800
		E.	150	70	70
		R.B.C.	3,700,000	4,000,000	4,700,000
		H.	74%	78%	84%
29	Chest.	L.	3,470	3,540	3,640
	Primary Malig-	P.	5,180	6,030	6,240
	nant Growth of	L.M.	320	730	420
	Sternum. (Not	E	50	50	104
	ulcerated.)	R.B.C.	5,800,000	5,400 000	5.300,000
		H.	98%	102%	100%
30	Jaw.	L.	1,960	2,070	..
	Epithelioma of	P.	·7,880	8,450	..
	Tongue.	L.M.	410	330	..
		E.	50	50	..
		R.B.C.	4,500,000	4,600,000	..
		H.	78%	78%	..
31	Jaw.	L.	3,720	3,950	4,090
	Recurrent Epithe-	P.	12,170	14,190	7,560
	lioma of Tongue.	L.M.	590	470	500
		E.	420	190	190
		R.B.C.	4,900,000	5,500,000	5,000,000
		H.	92%	100%	92%
32	Chest.	L.	1,830	2,980	3,070
	Carcinoma of	P.	7,140	3,040	4,690
	Breast. (Not ul-	L.M.	420	350	500
	cerated.)	E.	..	30	40
		R.B.C.	5,300,000	5,900,000	5,200,000
		H.	88%	88%	84%
33	Jaw.	L.	2,290	3,040	2,110
	Epithelioma of	P.	17.580	12,160	14,520
	Tongue.	L.M.	620	720	790
		E.	310	80	180
		R.B.C.	5,500,000	5,000,000	5,600,000
		H.	100%	96%	88%
34	Chest.	L.	1,020	1,720	2,510
	Mediastinal	P.	22,860	17,780	13.670
	Growth.	L.M.	1,420	710	1,040
		E.	..	..	90
		R.B.C.	6,000,000	5,600,000	5,400,000
		H.	82%	84%	78%
35	Neck.	L.	2,240	2,280	3,670
	Lymph-adenoma.	P.	8,290	8,660	16,220
		L.M.	560	400	410
		E.	110	60	100
		R.B.C.	5,600,000	5,500,000	5,700,000
		H.	112%	112%	114%
36	Face.	L.	2,810	4,400	..
	Epithelioma of	P.	9,780	12,770	..
	Tongue.	L.M.	600	1.110	..
		E.	200	190	..
		R B.C.	4,800,000	4,500,000	..
		H.	84%	80%	..

CONCLUSION.

The opportunity of using this large quantity of radium in the treatment of malignant disease has been invaluable.

The general trend of our experience in the application of the radium to malignant growths is that the majority of these growths

exhibit a high degree of resistance to the radiation, though some few types of growth e. g. lympho-sarcomata have seemed more susceptible, whereas others, for instance squamous epitheliomata, have proved more refractory.

The skin reactions following surface applications of the radium have been of the well-recognized character, and here again it may be said that the degree of reaction for the same length of exposure was very similar, but occasionally an unusually severe reaction followed the treatment.

The amount of pain due to the damage of the skin has been very variable; some patients have stated that they have had no pain at all, and that they would not have noticed the condition were it not for the serous discharge, while others have complained of considerable pain locally.

The degree of injury to the skin has seemed to be definitely influenced by the local vascular supply. In breast cases operated upon after treatment with the radium capsule, the wound has shown a tendency to heal slowly and to ulcerate in the places where the radiation has been most intense. In situations where the nutrition of the skin is poor on account of the proximity of malignant disease, a short exposure which usually does no injury has often caused vesication.

The effect of the radiation in such cases has been sometimes to hasten ulceration, and an additional factor influencing this result is the effect of the radiation on sepsis. There seems no doubt that, if a growth is already infected, the radiation produces favourable conditions for the growth of bacteria and, if at the same time the whole of the malignant growth has not been given sufficient exposure to delay the rate of division of the tumour cells, the condition produced leads to a rapid extension of the disease with breaking down of the skin. This has been particularly noticeable in cases of epithelioma of the tongue with secondary gland involvement.

One of the chief features of interest in the application of this large quantity of radium, apart from the direct effect upon the malignant growths, has been the general physiological reaction of the patient. Under the conditions adopted, the whole body received an appreciable amount of gamma radiation; during exposures which lasted 4 or 5 hours several patients complained of headache and sickness; subsequently a feeling of general malaise persisted in many cases for a few days.

Another observation of importance was that, occasionally, a marked œdema would supervene within 24 hours of the radium exposure; in several cases it was noticed that where œdema was present before the irradiation, this condition was much aggravated by the treatment; in one case to a dangerous extent. The general physiological effects following radium and X-ray exposures have received insufficient study in the past, and in view of the fact that such effects may play an important part in the reaction of the malignant growth itself when exposed to these agents, further investigation in this direction is much needed.

The experiences gained during the 20 months that we have had

the use of this large quantity of radium has convinced us that, in the treatment of malignant disease, the collaborate work of physician, surgeon, radiologist and pathologist is very necessary. The application of a lethal dose of radiation to actively proliferating and invading malignant cells is unlikely to be accomplished without due regard being paid to the pathology of the condition, to the physiological reaction of the normal tissues contiguous to the growth, to the opportunities for surgical intervention and to the various aspects of dosage and of radiological technique.   For extensive deep growths the quantity of radium required for adequate dosage is large in order that sufficient radiation may be given to the malignant cells; the possibility of lowering the resistance of the patient by this radiation has, however, to be borne in mind and guarded against.

In conclusion we have to deplore that Dr. Lyster did not live to continue the collaboration in an investigation which he initiated.   His death deprived us of an invaluable aid in the clinical work.

We are greatly indebted to the physicians and surgeons of the Middlesex Hospital for their cordial co-operation in this investigation.
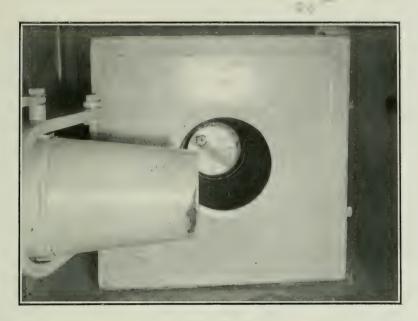
Fig. 1
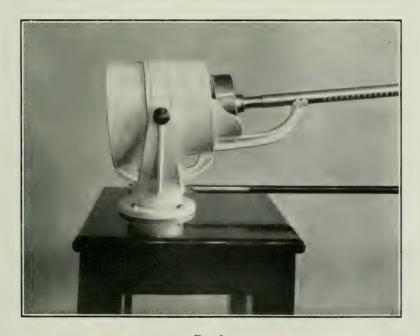
Fig. 2

2. ON THE HISTOLOGICAL CHANGES PRO-DUCED IN CERTAIN NEOPLASTIC AND NORMAL TISSUES IN MAN BY THE GAMMA RAYS OF RADIUM

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INTRODUCTION.

In another place, a description has been given of changes produced in frogs, rats, rabbits and cats by the action of the gamma rays of 5 grammes of radium bromide. It is impossible to present a correspondingly full picture of changes met with in man, mainly because the exigencies of medical practice have not allowed the materials for histological examination to be obtained at exactly comparable dates. In addition, particular importance attaches to the changes produced in new growths in man. Hence in the subsequent communication attention has been given to the normal tissues; in this communication, the chief description is confined to the new growths.

MATERIAL.

The material consists of:

    Six spheroidal cell carcinomata of breast,
    One squamous cell carcinoma of oesophagus,
    One rodent cancer of leg,
    One spindle cell sarcoma of thigh,
    One round cell sarcoma (? endothelioma) of pleura,
    One spindle cell sarcoma of rat (Jensen's rat sarcoma).

In addition, skin and some other human tissues are made subjects of short notes.

METHODS

As far as possible, the method of irradiation was the same in all cases. The brass box containing the radium was brought as nearly as possible in contact with the growth. Obviously, how-ever, the degree of irradiation undergone by the skin must have been approximately the same in all cases, but this is not true for the underlying new growth owing to the difference of depth from the surface at which it lay. Still less is it possible to institute an exact comparison between any tissue in one of the lower animals examined and man, because the entire animal was subjected to irradiation in the one case, whereas only a portion was subjected in the other. In no case was less than 4 weeks allowed to elapse between irradiation and removal of the mass and, on the other hand, the interval between irradiation and removal extended to 14 weeks (case 6).

The types of growth also varied within wide limits. In one there was a localized growth about three centimetres below the nipple. In another, there was a quadrilateral mass in the upper part of the breast. Both of these were operable cases, the remaining cases of breast tumour were frankly inoperable mammary carcinoma when they first came under observation, but as the result of the radium treatment their attachment to the subjacent tissues became loosened to such a degree that they returned into the operable category and an extensive, and as far as possible complete, amputation of breast with removal of axillary contents was carried out.

The cases are as follows :

Case 1. (A. C.) Operable carcinoma of breast. Radium exposure 5 hours. Amputation 42 days later.

Case 2. (F. G.) Doubtfully operable carcinoma of breast. Exposure to radium 6 hours. Amputation 45 days later.

Case 3. (F. R.) Inoperable carcinoma of breast and axilla. Radium exposure 6 hours. Amputation 64 days later.

Case 4. (M. R.) Operable carcinoma of breast. Radium exposure 5 hours. Amputation 78 days later.

Case 5. (M. A. H.) Inoperable carcinoma of breast of some years' duration. In December 1919 three radium tubes (total 150 milligrammes) were buried in tumour for 20 hours. One month later radium exposure to 5 grammes for 4 hours, and 4 months later still similar exposure for 5 hours. Amputation of breast 180 days after first and 73 days after second exposure to 5 grms.

Case 6. (A. G.) Inoperable carcinoma of breast and axilla. Radium exposure 6 hours, and 21 days later for 5 hours. Amputation of breast 119 days after first and 98 days after second exposure to radium.

Case 7. (M. T.) Squamous cell carcinoma of oesophagus. Radium exposure 5 hours, and 22 days later an additional 5 hours ; 15 days later three tubes buried in region of growth. Death 11 days later.

Case 8. (C. W.) Rodent cancer, large fungating growth on calf ; radium exposure 5 hours. Growth removed 28 days later.

Case 9. (J. P.) Large sarcoma of thigh treated by buried radium on several occasions. Radium exposure, 2 hours, and 19 days later a further two hours.

Case 10. (B. P.) Round-cell sarcoma (? endothelioma) of pleura. Radium exposure $7\frac{1}{2}$ hours at intervals over three days. Death 10 days later.

The histological material was hardened in 10% formol-saline, embedded in paraffin, stained with haematoxylin and eosin or with iron haematoxylin or sometimes counterstained with van Gieson.

Results.

Case 1. (A. C.) General appearances. There is great cellularity, no multinucleated cells seen, and no evidence of 'Indian file' arrangement. Cysts, lumina, degeneration, and mastitis are absent, and alveoli are of fair size.

The neoplastic cells are large, but show a very small amount of conglomerate, slightly granular cytoplasm, the bulk of the cytoplasm having disappeared entirely, so that nuclei lying almost naked within cell membranes are a conspicuous feature. The nuclei vary somewhat in size ; the majority are contracted, but swollen and vesicular forms are common. In the majority of cases staining is faint and diffuse, but small numbers of deeply stained forms are found. There is no particulate chromatin, although the distribution of the chromatin is frequently irregular in the nucleus. Nucleoli are uncommon, ghosts are rare, but forms of degeneration beyond ghosts are very common. Here and there is a sign of mitosis. The connective tissue is relatively considerable in amount, fibrillar, somewhat collagenous, and there is a moderately considerable infiltration of small cells in advance of the growth. (Fig. 1.)

Case 2. (F. G.) Cellularity is very considerable, and a small number of multinucleated cells is present. Some tendency towards 'Indian file' arrangement. No cysts, but some lumina and a small amount of degeneration ; no mastitis. Alveoli are small.

Neoplastic cells are large but contain a small amount of conglomerate hyaline cytoplasm, the greater portion of the cell contents having disappeared ; hence large numbers of the nuclei are left naked in the middle of the cell. The nuclei vary somewhat in shape and size and lack definition. The majority are swollen and a few are vesicular ; the number of contracted forms is small. Staining is moderately deep and diffuse ; a few faintly stained forms are found, but there is little irregularity in distribution of chromatin, and no particulate chromatin is found. Nucleoli are rare. The stroma is rather scanty, little fibrillar, and moderately collagenous. There is a moderate amount of small cell infiltration in advance of growth. Ghosts are moderately frequent, but forms at a further degree of degeneration are uncommon ; a few doubtful and some good mitotic figures are found. (Fig. 2.)

Case 3. (F. R.) The tissue is little cellular, and no multinucleated cells are found. 'Indian file' appearance is marked in certain parts of the tumour. There are no cysts, lumina, nor degeneration, but a considerable amount of mastitis is present in the neighbourhood. Alveoli are very small.

The cells of the new growth show a small amount of conglomerate hyaline cytoplasm and large numbers of cells in which the nucleus is naked within the cell membrane owing to the disappearance of the cytoplasm. Nuclei vary considerably in shape and size ; large numbers are contracted, none are definitely swollen or vesicular. Nuclear staining may be faint or deep, but in either case is diffuse, and no nucleolus is seen. Ghosts are frequent, but no more degenerate forms are found. There is no evidence of mitosis. Connective tissue is very considerable in amount and collagenous for the most part ; there is little fibrillation. A considerable small cell infiltration lies in advance of the new growth.

Case 4. (M. R.) Cellularity is considerable ; no multinucleated cells are seen. There is no 'Indian file' arrangement ; cysts, lumina, and degeneration are present in the neighbourhood. There is a moderate amount of mastitis. Alveoli are moderately large.

The cells of the new growth are of fair size, contain a moderate amount of conglomerate hyaline cytoplasm, show no vacuolation and little disappearance of cytoplasm, with the result that naked nuclei are unusual. The nucleus may be contracted or vesicular, but few actually swollen forms are seen ; staining is usually very faint or very deep, and in either case is diffuse, but a certain amount of irregularity in distribution of chromatin is seen; nucleoli are fairly common. Ghosts are few, and there is no evidence of more degenerated forms. A few mitoses are present in some of the sections. The connective tissue is scanty, sometimes fibrillar, sometimes collagenous ; there is little small cell infiltration.

Case 5. (M. A. H.) The tissue is highly cellular, and fair numbers of multinucleated cells are seen. There is a small amount of 'Indian file' arrangement and some foci of molecular degeneration ; no cysts nor lumina are present, and no surrounding mastitis. Alveoli are small.

Cells of the new growth show a large amount of conglomerate hyaline cytoplasm in which vacuolation is seen from time to time, but there is no complete disappearance of the cytoplasm of the cells. The nuclei vary within wide limits, some being contracted, others vacuolated or vesicular. Staining is very faint as a rule, but deeply stained forms are found, and irregular distribution of the chromatin or particulate chromatin is frequently seen. Large nucleoli are common. Ghosts are present in great numbers, and many forms more degenerate than ghosts are also seen ; an occasional mitosis is present.

The connective tissue varies in amount from place to place ; it is chiefly collagenous, but sometimes fibrillar. There is little small cell infiltration in advance of the growth. (Fig. 3.)

Case 6. (A. G.) Cellularity is very considerable, and multinucleated cells are present. There is a moderate amount of 'Indian file' arrangement ; cysts and lumina are numerous, and there is much mucoid degeneration in regions of the growth and within cysts, the latter being found in the region of mastitis. The alveoli are of considerable size.

The cells of the new growth show a moderate amount of conglomerate, hyaline, sometimes granular, cytoplasm in which vacuolation is common. The appearances differ in different slides, but complete disappearance of cytoplasm with a resulting naked condition of the nucleus within the cell membrane is sometimes very common. The nuclei themselves vary little in appearance, but the majority are swollen or vesicular, but some are contracted. Staining may be faint or deep, a small amount of dust-like chromatin is usual, and a nucleolus is often seen in the cells; nevertheless, diffusely stained nuclei are common. The number of ghosts, and of forms more degenerate than ghosts, vary from section to section. In tissue removed during life there are relatively few, but in breast tissue removed after death of the patient, they are numerous. There is no evidence of mitosis. The connective tissue is moderate in amount, a little collagenous but chiefly fibrillar. In some regions the growth appears to be rather of a columnar cell variety or to enclose ducts in which a certain amount of papillary growth has taken place. (Fig. 4.)

Case 7. (M. T.) Squamous cell carcinoma of oesophagus. The growth is of a mixed prickle cell and keratinizing variety, very few Malpighian cells being present. There are practically no prickles, but the amount of conglomerate cytoplasm is large, often foam-like, but irregular and vacuolated in many places. The cytoplasm gives the suggestion that it had formerly been swollen. The nuclei are round or oval, swollen, often vacuolated or vesicular, and sometimes show a definite split in the centre; they vary much in size and often present large nucleoli. As a rule, staining is very faint, but contracted, deeply stained forms may occur at the side of a lacuna. Ghosts are many, and may be large or represent fractions of degenerated nuclei. The epithelial pearls are much broken up, but offer no special features. The stroma is represented by loose contracted strands of fibrous tissue in which are plump or swollen, rather faintly-stained nuclei of connective tissue cells, and nuclei of small mononuclear cells, deeply stained lymphocytic nuclei, and a fair amount of deeply stained nuclear débris. The tissue in advance of the growth is definitely oedematous and the fibrils are swollen; in places it contains many nuclei, but small cell infiltration of the usual kind is scanty and limited to certain situations. No mitoses are seen, though a few irregular masses of intensely stained chromatin are found in places. (Fig. 5.)

Case 8. (C. W.) Rodent cancer of calf, perhaps with admixture of squamous cell carcinoma. The squamous portion shows a great development of the prickle cells (as in carcinoma of penis or vulva), but the epithelium does not extend any great depth into the subcutaneous tissue. From the base of some of the inter-papillary processes growth has taken place, the cells being of the Malpighian type and arranged in fairly orderly fashion as in Malpighian layer of the skin. In deeper parts the masses of cells are larger, but the arrangement of the peripheral layer is not orderly.

The cytoplasm of the neoplastic cells is conglomerate, rather foam-like, shows some lacunae, clefts, and ruptures. Nuclei are moderately well defined, vary somewhat in shape, but in the main are round or oval, rarely contracted, though sometimes elongated. Nuclear staining is always diffuse, but has a mossy appearance; it is moderately deep, but many pale forms and ghosts are seen; though the nuclei are swollen, vesicular forms are very exceptional. Nucleoli are not seen, broken-down nuclei are rare, but some intensely stained, angular contracted forms are found (Fig. 6). In the parts that are definitely squamous, the prickle cells are often well marked and show a good prickle layer. Nuclei are large, oval, pale, often nucleolated, and in some places swollen. In places, collections of cells and nuclei are undergoing degeneration, and take the oxyphil stain. Some almost vesicular forms are found. Close to the surface are appearances barely suggestive of pearls, but none are found in the depths. Subcutaneous connective tissue is the seat of chronic inflammation and shows many pale elongated nuclei of endothelial cells and fibroblasts, and small mononuclear cells with moderately dark nuclei. Ghost nuclei of all kinds are found, and some pale broken-down forms, but no considerable amount of débris; definitely lymphocytic nuclei are few in number. In the deeper parts of the subcutaneous tissue are many plasma cells. Superficially, there is a small amount of purely fibrillar connective tissue, but in the deeper parts the connective tissue is much denser, more voluminous and collagenous, and contains fewer cells.

In a portion of the same tissue removed prior to radium treatment there is a limited layer of superficial squamous epithelium not covering the entire section, beneath which are irregular masses of loose, highly cellular material Between these masses are broad strands of moderately dense connective tissue. In the strictly squamous region the Malpighian layer is well marked, and is succeeded by two or three layers of prickle cells in which the prickle space is not well marked. The cytoplasm of the cells is cloudy and hyaline. The nuclei are very pale and nucleolated, the nucleoli being large, usually single, sometimes double and intensely stained ; the rest of the nucleus has no particulate chromatin. Above the prickle cell layers are a few superficial stratified layers. The inter-papillary processes are irregular, but there is no evidence of invasion of the deeper parts, nor are cell nests present. The masses of neoplastic cells in the subcutaneous tissue are arranged in a loose meshwork with large rounded spaces similar to those met with in areolar tissue. The cytoplasm of the cells is conglomerate, scanty, and fibrillar. Nuclei are very irregular in shape ; the majority are intensely and diffusely stained, but some are swollen and appear to be oedematous. Around the periphery of the cell masses the nuclei are arranged in an irregular palisade fashion. A few paler nuclei are found throughout the mass, but there are no ghosts nor fragmented nuclei. Intensely stained irregular masses suggestive of mitosis are not infrequent. The interstitial material consists of young cellular con-nective tissue, in which are varying numbers of polymorphonuclear leucocytes ; these cells are particularly numerous in the neighbourhood of the denuded surface of the mass. The appearances are those of oedematous rodent cancer.

Case 9. (J. P.) Spindle cell sarcoma of thigh. In this case a portion of tissue was obtained prior to the exposure of the mass to the gamma radiation of 5 grammes, but since the tumour itself had previously been treated by buried radium it must not be assumed that the appearances are normal.

Before exposure to 5 grammes the tissue presents no signs of swelling, but on the contrary appears to be contracted as the result of preservation. Thus some specimens show much shrinkage and disappearance of cytoplasm, remnants of which are represented by fine filaments between more or less naked nuclei. The nuclei are irregular in shape, show a little contraction, and stain moderately and diffusely. A few pale forms, possibly ghosts, are present. In some portions of the tumour there is complete degeneration, the tissue presenting merely filaments and outlines of cells without nuclear staining and taking but little of the plasmatic stain. The structure of these degenerated parts appears to be identical with that of parts that stain satisfactorily.

After treatment with 5 grammes the sections show some vacuolation of con-glomerate cytoplasm, possibly due to contraction during preparation. The cytoplasm is very soft and lightly stained. The nuclei are irregularly spindle shaped and show some contraction of normally plump forms. Distribution of chromatin may be irregular. There is little vacuolation, staining is very faint in general, and almost diffuse, so that no statement can be made with regard to ghosts. In other sections there is not the same amount of contraction, but the nuclei are pale and plump, clefts between the nuclei occur, and some of the nuclei appear to be naked, no cell membranes being visible. In one degenerated part there is nothing more than delicate gelatinous connective tissue with numerous large capillary blood-vessels full of blood ; no leucocytes are seen. (Fig. 7.)

Case 10. (B. P.) Round cell sarcoma (? endothelioma) of pleura. The tissue is not greatly circular, and presents strands of cells in a dense fibrous tissue stroma. The stroma shows many clefts in which are a few contracted cells, and from its appearance might have been very soft or oedematous previous to preparation. In the growth itself the cell cytoplasm is conglomerate and almost invisible, but is not absolutely scanty. The nuclei are round, vesicular or vacuolated, pale, and present very little chromatin except in intensely contracted forms, and many ghosts and vesicular fractions of nuclei are common. To a small extent cytoplasm has disappeared from the cells, leaving the nuclei naked within the cell membrane. In some regions are definite areas with no visible cells.

Case 11. Jensen's rat sarcoma. Grafts were inoculated, the animals were irradiated for $3\frac{1}{2}$ hours, and grafts were removed on the third, fifth, and eleventh day for microscopic examination.

Third day. Definition is poor and the cells have a mossy appearance. Some large lacunae are present, as if areolar tissue had been invaded. There is some spacing between the cells. Cytoplasm is voluminous, hyaline, and the cells are irregular in shape, but spindle shaped in the main. There is no vacuolation. The nuclei are large, ill defined, pale; chromatin is very scanty and when present is irregularly arranged, often collected in the centre of the nucleus and may simulate a nucleolus. Nuclei vary greatly in size, and many are intensely vesicular. Ghosts and degenerated pale forms are numerous, even close up to the edge of the graft; contracted and deeply stained nuclei are very few. Small numbers of small mononuclear cells are included in the outer flattened layers, but there is practically no general peripheral lymphocytosis. The connective tissue is much swollen and fragmented, but not collagenous; mitosis is very doubtful. The peripheral blood-vessels show very few leucocytes, and the nature of these is uncertain. Fibres of voluntary muscle are swollen, hyaline, show no striation, but good evidences of contraction; their nuclei are faint and diffuse, irregular in shape, few in number, and often ghost-like. Around the graft many granulation tissue capillaries may be present.

Fifth day. (*Specimen A.*) Definition is sharp, the central part of the graft is less cellular, and more contracted material is present. The nuclei are more deeply stained, more contracted, and far fewer in number. The cytoplasm is conglomerate in the main. At the periphery there is granulation tissue with many capillary blood-vessels and some large masses resembling giant cells. The granulation tissue looks normal and healthy, it consists of spindle cells with many small mononuclear cells; the cytoplasm is conglomerate and not vacuolated. It is impossible to distinguish young rat-sarcoma cells from young connective tissue cells. Blood-vessels are numerous, full of red blood corpuscles, but show very few leucocytes (possibly lymphocytes). Muscular fibres are flaccid and hyaline, striation is present in some fibres, but is very poor as a rule. Muscle nuclei are pale, almost diffuse, but a little dust-like chromatin may be present. Their shape is oval, with practically no contraction, and they may be a little swollen and vesicular where the fibre is disappearing. No mitoses are seen.

(*Specimen B.*) Muscular tissue is infiltrated. Nuclei of graft are oval or spindle shaped, of muscle are usually vesicular. Staining is pale and ill-defined. It is doubtful whether mitoses are present.

(*Specimen C.*) There is great irregularity and a deeper staining of nuclei; many small round nuclei are present, possibly due to the plane of section. Large degenerated cells and nuclei and many ghosts are present, and there is some vacuolation of cytoplasm with implantation of crescentic deeply stained nuclei on the side of the vacuoles. Granulation tissue is not so evident; the connective tissue is much swollen, and beneath the skin is collagenous. No small cell infiltration is recognized.

Eleventh day. There is good definition but great variability in size and shape of the nuclei. Slight clefts are found between cells, and the mass is permeated by some small capillary blood-vessels. Many ghosts are present, and many ghost-like fractions of nuclei. Here and there, towards the edge of the graft, large oval, plump nuclei with much deep particulate chromatin are found. Intermingled with these are small round deeply stained nuclei (? lymphocytic). Very little granulation tissue is present. There is much extravasated blood in the periphery. The connective tissue is finely fibrillar, much broken, and the larger fibres are a little swollen. Few cells are present in the meshwork. There are many small blood-vessels, but these are usually empty; a few leucocytes are seen.

In addition to the masses of new growth described above, certain tissues have become available from some of the cases which may be compared with materials derived from the lower animals described elsewhere.

Skin.

In cases 2, 3, 5, and 6 the gamma irradiation had been sufficiently severe to lead, after an interval of about three weeks, to

a superficial vesication and ulceration of the skin. Sections of this area with the skin in the periphery were examined.

In case 2 the floor of the ulcer shows no squamous epithelium, but is composed of a moderately dense, chronically inflamed subcutaneous tissue in which are numerous small blood-vessels, considerable numbers of broken-down, deeply stained nuclei and a few large nuclei, apparently endothelial in character; no poly-morphonuclear leucocytes nor definite lymphocytes are present. These cells occupy no great depth of tissue, but beneath them there is a collagenous connective tissue. The edge of the ulcer is fairly sharply limited by the presence of squamous epithelium, and in this region, i. e. the periphery, the squamous epithelium cells have lost much of their definition and the nuclei are contracted and lie in lacunae. There is some tendency to stripping of the superficial keratinous layers; the Malpighian layer is irregular and ill defined, and the corium contains a few more cells than normally, but the difference is not pronounced. In the deeper part of the corium the connective tissue is collagenous.

In case 3 there is no essential difference, but the destruction of the epidermis is more considerable; there is less cellular infiltration of the upper layers of the corium, though some of the small vessels and their surrounding connective tissue are crammed with small round cells, and there is definite great collagenous modification of the connective tissue. Apart from the foci described, the corium is simply acellular.

In case 5 there is a greater amount of cellularity beneath the denuded surface, and many of the cells may be lymphocytes; in addition, there is much nuclear débris and some extravasated blood. Such small cell infiltration as exists beneath the persistent squamous epithelium is moderate in amount and is associated with oedema, probably some cells present in this region are plasma cells. In the connective tissue surrounding the small vessels of the deeper part of the corium there are accumulations of plasma, small mononuclear and endothelial cells, but apart from these the deeper layers of the corium are relatively acellular and the connective tissue is highly collagenous.

In case 6, over the denuded area, there is an irregular degenerated heaped-up mass in which structureless material and broken-down nuclei alone are visible. Beneath the ulcer there is oedematous and somewhat cellular connective tissue in which the fibrils have undergone oedematous rather than collagenous change; at the periphery of the ulcer the squamous epithelium is very irregular in arrangement, the nuclei are shrunken and lie in lacunae. The details of the cells are not distinguishable, and staining as a whole is poor. The corium is oedematous but fibrillar, and the fibrillae branch in all directions, they include within their mesh-work many degenerated nuclei and a few endothelial nuclei which appear to be normal. Further away, the epidermis still stains faintly and lacks definition, but the outlines of prickle cells become recognizable, nevertheless there is great irregularity and contraction of the nuclei and they tend

to lie in clear spaces. The corium is slightly cellular and shows a smaller proportion of degenerated cells than towards the centre and larger numbers of elongated connective tissue cells. Here the stroma is definitely swollen and some of the fibrils appear to be collagenous.

Voluntary Muscle.

Voluntary muscle has been examined after embedding in paraffin, and also after hardening in formol-saline and freezing; in the latter instance it was stained with Sudan or scarlet.

In case 4 the great pectoral muscle shows variation in the degree to which the plasmatic stain was taken, but striation is fairly good and the fibres not contracted. Some translucency was seen, and a stained albuminous deposit was present over most of the fibres. The nuclei, when viewed on the flat, are oval or almost round in shape, very faintly and diffusely stained, and only in rare instances show particulate chromatin. Viewed in profile, they are rod shaped, rarely linear, and more deeply stained. There is no noteworthy interfibrillar space, nor are adventitious cells or material present.

In frozen sections, striation is better, some of the fibres taking the stain to a definite degree, and in a few there are fine particulate globules of lipoid substance, which may be located chiefly in the striae or their distribution may be more irregular. Large fat globules are not found.

In case 5, in paraffin sections, plasmatic staining is fairly deep. The muscle fibres are arranged in parallel rows, their contractile material is hyaline, very little striation is visible, and the nuclei when seen on the flat are oval or almost circular in a large number of cases. The nuclei contain very little, diffusely stained, chromatin, and in many instances are so pale that they are barely recognizable. In other portions of the field staining is better, and the nuclei, though swollen, may show moderately deep staining and dustlike chromatin.

In frozen sections striation is better though still very poor, fibres take a certain amount of yellow stain, and in some cases the fibres are more deeply stained than their neighbours. Throughout the specimen there is a fine dust-like deposit of deep red or orange material which is more marked in some fibres than in others.

In case 6 frozen sections of muscle show excellent striation, no special staining of fibres and no deposition of lipoid globules. Specimens embedded in paraffin and stained with iron haematoxylin show good striation, and fibres are split into their constituent fibrils; there is no translucency and the fibres are not swollen. Intermuscular spaces are of normal dimensions and contain no adventitious cells or material.

Miscellaneous.

In case 6 the patient died from intestinal obstruction five weeks after removal of the breast. At the autopsy a mass was

found in the intestine which on examination proved to be columnar cell carcinoma, quite unlike the primary growth in the breast. Reference has already been made to the appearances of mammary growth removed after death.

Spleen (Case 7).

In case 7 the spleen was highly cellular, but the cells present were almost entirely of the endothelial and small mononuclear type, lymphocytes were few in number and, when found, usually constituted small foci in the neighbourhood of a blood-vessel. Definition and staining of the nuclei was good, but a certain number of degenerated forms were present, and there was definite evidence of nuclear débris. No phagocytic cells were seen; the red blood corpuscles in the organ were fairly well preserved.

Liver (Case 7).

Capillaries of liver are widely dilated and contain a moderate amount of blood. Hepatic cells are sharply defined and contracted. The cytoplasm is hyaline and varies in density in different places, sometimes it carries a small amount of pale yellow pigment, but there are no lacunae suggestive of the former presence of fat. The granular pigment appears to bear no special relation to the position of blood-vessels.

The nuclei vary much in degree of definition, ghost-like, and even more degenerate, forms being numerous. There is no great variation in size of nuclei, though some unusually large forms are found. In well-marked nuclei there is a small amount of intensely stained dust-like chromatin, and a nucleolus which frequently is eccentric. The nuclei are not actually vesicular, but are less deeply stained in the centre. There is an increase of fibrous tissue in the organ, particularly around the blood-vessels. The bile ducts show some proliferation of epithelium. In frozen sections stained with Sudan there is considerable evidence of congestion; no fat is found.

Kidney (Case 7).

The organ in general is congested, the capillaries in the glomerular tuft are dilated and may be empty or contain red blood corpuscles. The lining endothelium of Bowman's capsule is fairly persistent and well marked, though there is variation in the number of nuclei seen in individual glomeruli, and many of the nuclei are swollen. The glomerular space may contain a small amount of granular material, but is generally empty. In the convoluted tubules the cytoplasm of the renal cells is cloudy, or partially foam-like. There is no marked breaking down, but small amounts of coagulated material are found in the lumina of the tubules. The outlines of the cells and the basement membrane are not distinct. The nuclei vary much in intensity of staining, and some ghosts are present, but no tracts of cytoplasm are found without nuclei, and degenerate forms more advanced than ghosts

are relatively infrequent ; there are no casts.   In the conducting
tubules the cytoplasm has often disappeared to a greater or less
extent so that the nuclei lie in lacunae.   Actual disintegration of
the epithelium also occurs to some extent.   Interstitial substance
is swollen and hyaline, particularly in the papilla, where it pre-
sents a more or less homogeneous material with swollen connec-
tive tissue and other nuclei.   In this material are circular or
elongated spaces occasionally lined by a regular layer of epi-
thelium, more frequently containing that epithelium desquamated
and contracted in the centre of the space.

Frozen sections stained with Sudan show fairly numerous
portions of tubules, particularly in the cortical region, in which
there is a considerable deposit of dust-like lipoid material.   A
similar deposit of lipoid material occurs also, but to a less
extent, in the conducting tubules.   Under Nile blue sulphate
stain, no regions are found in the kidney having lilac or pink
staining.

Summary and Conclusions.

In most cases it is impossible or unsatisfactory to compare
the same tumours before and after exposure to the gamma
radiation, but it is possible to obtain some idea of the effects
of that radiation by contrasting, on the one hand, the appearance
of tumours that had received one exposure of 5–6 hours with
those that had none, and on the other hand, those which had
received two exposures with those that had had only one.   In
the case of mammary tumours (spheroidal cell carcinoma) the
following deductions are made :

The effects of one exposure lasting 5–6 hours to the gamma
radiations from 5 grammes of radium bromide are partly general
and partly cellular.   As general effects, it is noted that cellularity
is somewhat considerable, that degenerate masses are rare, that
multinucleated cells are very few, that fibrous tissue is present in
considerable amount, is collagenous and little fibrillar, that it
shows no proliferation of connective tissue cells, that ' Indian
file ' arrangement is very slight, and that small cell infiltration
in advance of the growth is slight to moderate.

In respect of the cells it appears that the cells are large, that
the quantity of cytoplasm is slightly hyaline or slightly granular,
rarely vacuolated, but that frequently cytoplasm has disappeared
entirely leaving the nuclei naked.   The nuclei are slightly
variable in shape, more often contracted than swollen, and
rarely are vesicular.   Staining is faint or deep, but almost always
is diffuse and rarely is irregular.   Nucleoli are very uncommon ;
degenerated forms more advanced than ghosts are rare, but ghosts
are fairly common.   Mitosis is extremely uncommon.

The effects of two exposures, as contrasted with one exposure,
are as follows :

As general effects it is noted that cellularity is greater, that
degenerate masses are more common, that more multinucleated
cells are seen, that ' Indian file ' arrangement is definitely greater,
that fibrous tissue is less conspicuous, less collagenous, more

fibrillar, and small cell infiltration in advance of the growth is less marked.

In respect of the cells, more cytoplasm is present, it is more frequently hyaline, less frequently granular, more frequently is vacuolated, less frequently has complete disappearance occurred leaving the nucleus naked within the cell membrane. The nuclei themselves are more variable in shape, more contracted and more swollen forms are present, and considerably more vesicular forms. Staining is rather fainter, but there is a much greater tendency to the presence of particulate chromatin and nucleoli, and small tendency to diffuse and irregular staining. In respect of degenerate forms, ghosts are a little more common, but forms more degenerate than ghosts are definitely more uncommon. Mitoses are even fewer than under conditions of a single exposure.

As a result of exposure to a considerable degree of gamma radiation, therefore, it would appear :

(1) That there is disappearance of cytoplasm from the neoplastic cells more marked after a single than after two exposures.

(2) That the intranuclear relations are altered, as is shown by the frequent presence of swollen, vesicular, or greatly contracted forms, by numerous ghost nuclei or even more degenerate forms, by the great variability of staining reactions, and by the great rarity of mitotic figures.

(3) That there is increased tendency to the occurrence of localized degeneration of neoplastic cell masses.

(4) That the connective tissue fibres permeating the growth become collagenous in greater or less extent.

(5) That the appearance of lymphocytic or small mononuclear cells, usually found in advance of the growing edge of a malignant neoplasm, is less extensive than usual and may be wanting altogether.

(6) That there is no evidence of proliferative change in connective tissue or endothelium.

In the two cases of sqamous cell growth examined, appearances were substantially the same. In the characteristic squamous cells, whether neoplastic or of skin, the nuclei showed great faintness of staining, were often nucleolated, vacuolated or vesicular, or were contracted and lay in a lacuna, but ghost nuclei were frequent ; mitoses were practically absent. On the other hand, there was not the same disappearance of cytoplasm from the neoplastic cells. A collagenous change of the connective tissue fibrils was marked.

In a squamous cell growth of the rodent cancer type, the nuclei of the malignant cells were swollen and stained more deeply, but vesicular forms were very rare, and nucleoli were not seen ; on the other hand, many pale nuclei and ghosts were present, the cytoplasm was conglomerate and foam-like, but showed clefts. Comparing the same growth of rodent type before and after exposure to the radium, the gamma radiation appears to have led, in cells of the Malpighian type, to nuclear swelling, the occurrence of many ghosts and absence of mitosis, and, in connective tissue, to marked collagenous change of the fibres.

Sarcomata. The microscopical appearances offer a great contrast to those met with in carcinomata, for nuclei lying naked at some distance from the surrounding cell membrane are not seen in the sarcomata, and vacuolation of the cytoplasm is rare.

It must not be concluded from this that disappearance of cytoplasm, which is so common in the case of the carcinoma cell, does not occur in the sarcoma. From the fact that naked sarcoma nuclei are seen, it is probable that such disappearance of cytoplasm takes place, but it is far less common and does not lead to the production of a characteristic picture. Nuclei of sarcomata are swollen, but very rarely are vacuolated or vesicular, though such a condition may characterize the majority of nuclei in a good case; usually staining is so faint that a general ghost-like appearance of the nuclei results, but in some cases definite ghost nuclei, or fractions of nuclei, are seen amongst nuclei in which the staining is moderately deep.

Miscellaneous. The number of cases is too few for dogmatic statement, but the following conditions have been observed in man and in certain lower animals after exposure to the gamma radiation of 5 grammes of radium bromide :

(1) Lipoid deposit in striated muscle fibres.

(2) Lipoid deposit in cells lining tubules of kidney.

(3) Great deficiency of lymphocytes in spleen,

(4) Dilatation of hepatic capillaries and ghost-like condition or other degenerative change culminating in disappearance of the intrinsic nuclei of the liver.

In the case of all the neoplasms described above, a diminution in volume of the mass occurred subsequent to the irradiation.

In case 1 this was so considerable that the breast tumour seemed to have disappeared, and in case 8 actual measurements of the tumour were conclusive on the point. In other cases the fixed growth became mobile.

As to the actual explanation of these changes, there is some difficulty. In case 1 the histological appearances after irradiation indicate so considerable a removal of cytoplasm that great flaccidity must have resulted. Quite apart from the question whether neoplastic cells in such a condition are still viable or not, it appears probable that some cases in which growths have been said to vanish fall into this category. On the other hand, in case 8, the histological appearances are not consistent with this explanation, and it is probable that an actual abolition of some of the new growth cells has occurred. It is noteworthy that this case was one of rodent cancer, a condition in which radiation treatment is recognized to be of great value.

Finally, the gamma radiation may act chiefly on the neoplastic nucleus, or chiefly on neoplastic cytoplasm, or both elements of the cell may suffer together; but these experiments give no support to the view that the changes undergone by new growths under radium and X-rays are essentially due to strangulation from an increased proliferation of the connective tissue elements, or essentially due to starvation from increased proliferation of endothelial cells within the nutritive blood-vessels.
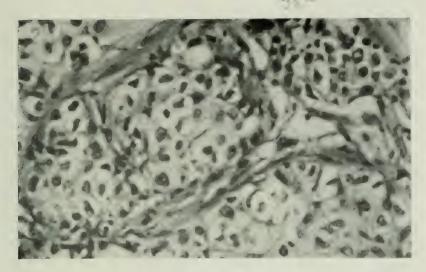
Fig. 1 (Case 1, A. C.). Spheroidal cell carcinoma of breast. Irradiated once. For details of radium exposure see text. Note (1) the extensive disappearance of cytoplasm from the neoplastic cells, (2) the irregularity in shape of the nuclei, of which the majority are contracted and deeply stained and a few are pale and ghost-like, (3) the presence of nuclear fractions, and (4) the collagenous condition of the connective tissue. Paraffin, haematoxylin, eosin. × 310.
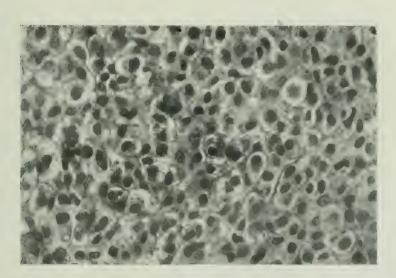
Fig. 2 (Case 2, F. G.). Spheroidal cell carcinoma of breast close to growing edge. Irradiated once. For details of radium exposure see text. Note (1) early disappearance of cytoplasm from the cells, (2) swollen condition of nuclei, (3) relative evenness in size and depth of staining of nuclei. Paraffin, haematoxylin, van Gieson. × 310.
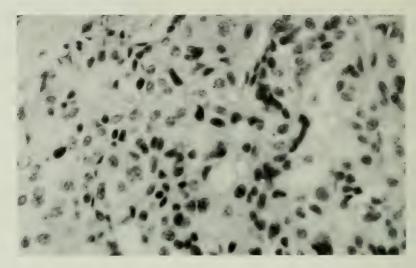
FIG. 3 (Case 5, M. A. H.). Spheroidal cell carcinoma of breast. Irradiated twice. For details of radium exposure see text. Note (1) the relatively large amount of cytoplasm and its persistence as shown by the lack of clear spaces around nuclei, (2) swelling and variation in size of the nuclei, (3) many pale (ghost) forms. The connective tissue in this region is gelatinous but fibrillar and alveolar arrangement of the growth is little marked. Paraffin, haematoxylin, eosin. × 310.
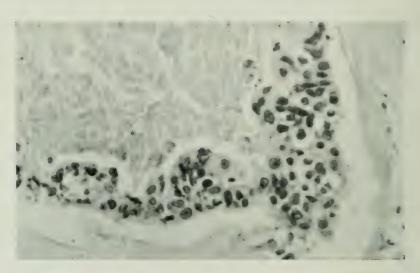
FIG. 4 (Case 6, A. G.). Spheroidal cell carcinoma of breast. Irradiated twice. For details of radium exposure see text. Portions of an alveolus. Note (1) frequent disappearance of cytoplasm leaving a naked nucleus, 2, variability in size and depth of nuclear staining, (3 occasional ghost nuclei, 4 central mass of degenerated cells, 5 the connective tissue is intensely collagenous and the nuclei are few and contracted. Paraffin, haematoxylin, eosin. × 310.
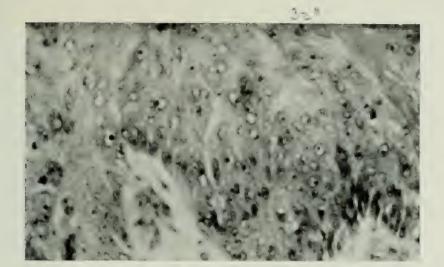
Fig. 5 (Case 7, M. T.). Squamous cell carcinoma of oesophagus. Irradiated twice. For details of radium exposure see text. Portion of an epithelial process. Note (1) the poor development of the Malpighian cells, (2) swelling of prickle cells and obliteration of prickle space, (3) vesicular character and variation in size of nuclei, (4) intensely stained nucleolus. Paraffin, iron haematoxylin. × 310.
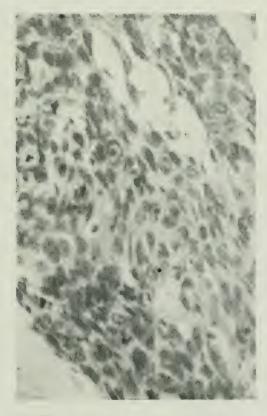
Fig. 6 (Case 8, C. W.). Rodent cancer of leg. Irradiated once. For details of radium exposure see text. Note (1) conglomerate cytoplasm, (2) fenestration, (3) swollen, diffusely stained nuclei mixed with elongated and broken forms, (4) ghost nuclei. Paraffin, haematoxylin, eosin. × 310.
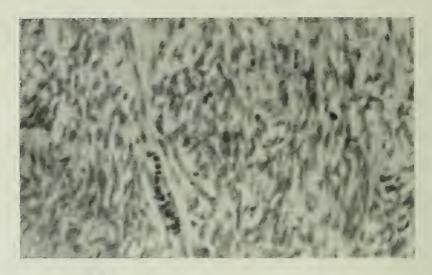
FIG. 7 (Case 9, J. P.). Spindle cell sarcoma of thigh. For details of radium treatment see text. Note (1) conglomerate homogeneous cytoplasm, (2) great irregularity in size and shape and poor definition of nuclei, 3 pale diffuse nuclear staining. Paraffin, haematoxylin, eosin. × 310.
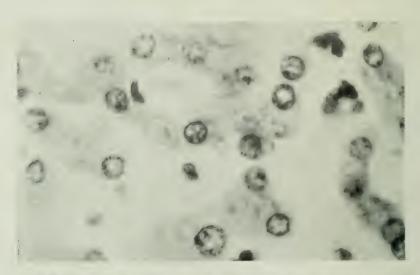
FIG. 8 (Case 7, M. T.). Liver. To show degenerative changes of nuclei. In the centre of the field is one approximately normal nucleus of a hepatic cell. Elsewhere are many ghost nuclei in varying degrees of degeneration. Some tracts of the liver tissue appear to be devoid of nucleus until carefully examined, and in others a little chromatin débris alone is present. Some of the nuclei show central absence of chromatin and are becoming vesicular. The wide spaces are dilated blood capillaries. Paraffin, haematoxylin, eosin. × 900.

3. ON THE HISTOLOGICAL AND SOME OTHER CHANGES PRODUCED IN ANIMALS BY EXPOSURE TO THE GAMMA RAYS OF RADIUM

by

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CONTENTS

INTRODUCTION

THE appearances described in the following pages are derived from the examination of twenty frogs, twenty-eight rats, fifteen rabbits, and nine cats exposed to the gamma radiation of 5 grammes of hydrated radium bromide under different conditions. The research is essentially histological, but in the rabbits and in one cat repeated blood examinations were made during life for comparison with blood changes observed in microscopic sections. These appearances were correlated with changes observed in bone-marrow, and described by Dr. C. Price Jones in a separate report. A separate report is also made by Dr. Morowoka and Sir F. W. Mott upon the appearances found in the brains of the

animals. In a few cases special phenomena were observed during life of the animal or were recognized after death, but usually nothing noteworthy occurred.

This part of the research was carried out in the Cancer Research Laboratories of the Middlesex Hospital. I have much pleasure in acknowledging the help give me by Dr. J. A. Murray on mitochondria and Mr. J. W. McNee on fatty changes.

METHODS

The animals were exposed to the radium somewhat differently. Distances were referred to the midpoint of the animal in a crouching position. Rats were distant 4 cm. from the radium and were irradiated from the side; frogs, rabbits, and cats were irradiated from above, frogs being 4 cm. and rabbits and cats 15 cm. from the radium. The effect of these differences in distance is discussed later (p. 109).

The animals were usually killed by breaking the neck, either immediately after exposure or after some period of survival, but occasionally they died under radium exposure. The routine methods adopted with tissues selected for examination were (1) hardening for 24 hours in 10 per cent. neutral formol saline, (2) washing in running water for several hours, (3) graduated alcohols, (4) xylol, (5) paraffin, (6) haematoxylin and eosin. Special preservation methods (e. g. formol Müller, osmic acid) and staining methods (e. g. Sudan, scarlet, Nile-blue, osmic acid Pappenheim) were used in certain cases.

The tissues examined were blood, muscle, connective tissue, endothelium, liver, spleen, pancreas, kidney, adrenal, stomach and intestine, generative system, lung and air passages. thyroid and parathyroid, paraortic tissue (rat), salivary gland, lymphatic gland, and bone-marrow. In a few instances not all these tissues were available or examined. As types of striated muscle were selected the muscles of the anterior abdominal wall, the adductor magnus, the biceps, and occasionally deep muscles of the neck and thorax. As non-striated types have been chosen the external, internal, and mucosal muscular coats of stomach, duodenum, jejunum, ileum, colon, rectum, the muscular coats of arteries and arterioles, and, in females, the uterus and Fallopian tube. In the case of heart, various parts have been taken without special selection.

Endothelium was examined as it occurs over stomach, duodenum, jejunum, ileum, colon, rectum, spleen, sex glands, lung, large and small blood-vessels, and the appearances were recorded in each instance. The gastro-intestinal mucous membrane was examined in the regions of stomach and intestine mentioned above, and the possibility that the changes were due to post-mortem digestion, was excluded by opening the gut in some instances directly the animal was killed.

For comparison the tissues of 5 normal frogs, 4 normal rats, 1 normal rabbit, and 1 normal cat were prepared, examined, and described in the same way as the radiated animals. Protocols of the normal rabbit and cat are not included here.

HISTOLOGICAL CHANGES IN THE FROG

THE NORMAL FROG.

From an examination of five non-radiated frogs. the following standard conditions have been determined. Certain of these frogs showed the presence of animal parasites in the lungs, but, inasmuch as similar parasites are found in radiated animals, this factor may be neglected in determining the effects of irradiation itself.

Blood.

The red blood corpuscles are of good size and shape. The nuclei are fairly well stained when viewed on the flat, intensely stained when seen in profile, and occupy the middle third of the cell or a little more. In the majority of cases some leucocytes and a few deeply stained free nuclei are present. No thrombosis is present.

Striated Muscle.

The contractile material stains moderately deeply and shows fair striation. Usually it is fibrillar. but may be translucent in places. The nuclei are rods with rounded ends about 9 times as long as broad and faintly stained. Usually a small amount of dust-like chromatin is present. Fairly wide intermuscular spaces are present and are devoid of adventitious cells or material.

In frozen specimens. striation is good where the fibres lie straight, but, where they are contorted, striation is poor or invisible. No lipoid is present.

Unstriated Muscle.

Unstriated muscle is well developed. In the stomach it is occasionally translucent but usually hyaline and homogeneous and stains well. A few clefts may be present. The nuclei vary in size and shape, but in most cases they are long rods staining well and perhaps showing a little vacuolation. There is no markedly wide intermuscular space. In intestine the appearances are substantially the same. In lung the contractile material is fibrillar, and usually hyaline : the nuclei are rods of various lengths that stain moderately deeply. In artery the contractile material is fibrillar, but occasionally it is homogeneous and shows slight vacuolation and a few clefts. The nuclei are irregular in shape and staining, and may show slight vacuolation.

Cardiac Muscle

Cardiac muscle shows good fibrillation and practically no striation. The contractile material is hyaline or very slightly granular. Interfibrillar spaces are often present. The nuclei are short thick rods. 6–7 times as long as broad, and show a small amount of dust-like or particulate chromatin. or a nucleolus on a faintly stained basis. Staining of nuclei is fairly good.

Connective Tissue.

Connective tissue is myxomatous as a rule. The fibrils are delicate and the nuclei vary in shape or staining according as they are connective tissue or endothelial. In the intestinal villi the connective tissue is vacuolated or oedematous.

Endothelium.

Over stomach and intestine the endothelial layer is well preserved. The nuclei, when viewed on the flat, are round or oval and faintly and diffusely stained, when seen in profile, are linear and deeply and diffusely stained. Over spleen, heart, kidney, and lung, the endothelium is fairly well preserved, and the nuclei are somewhat irregular in shape and staining. In spleen pulp and over alveoli of lung, the nuclei are very irregular in shape, pale in spleen, rather deeply stained in lung. In large blood-vessels the endothelium is well preserved, the nuclei are elongated and stain deeply. In small blood-vessels the preservation is not quite so good and the nuclei are more irregular in shape but stain deeply.

Liver.

The tissue shows large dilated blood-vessels and capillaries, but is fairly coherent. The cells are polygonal. The cytoplasm is definitely oxyphil, hyaline but with a varying degree of granularity, sometimes is very much diminished, sometimes slightly vacuolated. The nuclei are even in size and round; a fair amount of particulate chromatin is present. Definition is good. No 'ghosts' or degenerated forms are seen. In the bile ducts there is a columnar epithelium of which the nuclei stain moderately deeply, and are irregular in shape. Frozen sections show a small amount of lipoid, and pigment is scattered throughout the tissue in varying amounts.

Spleen.

Red blood corpuscles are present in great numbers, and fair numbers of non-haemal cells are also present. Cytoplasm can rarely be distinguished. Practically no Malpighian corpuscles nor germinal areas are visible. The nuclei are irregular in shape and staining, probably the majority are endothelial. A small amount of black pigment is scattered through the tissue.

Pancreas. (One example.)

Irregular acinous arrangement with ducts and blood-vessels. Cells are polyhedral and sharply defined. The cytoplasm is basophil, hyaline, and the nuclei are round, deeply and diffusely stained and basally placed. No islands of Langerhans. The ducts are surrounded by delicate connective tissue and are lined by a columnar epithelium.

Kidney.

The glomerular tufts are contracted but the capillaries are widely dilated and show few red blood corpuscles. Nuclei are numerous, irregular in shape, and usually stain intensely. The

endothelium lining Bowman's capsule is good as a rule, and the glomerular space is empty. The convoluted tubules show an irregular epithelium and lumen. The cytoplasm of the cells is mainly hyaline and occasionally somewhat broken down. The nuclei are irregular in shape and staining : there is a slight amount of particulate chromatin and perhaps some vacuolation. In the conducting tubules the epithelial lining is generally good, the cytoplasm of the cells is hyaline or granular, but the nuclei vary in shape and depth of staining. No 'ghost' forms are seen in the renal epithelium. The stroma is scanty, but the nuclei stain moderately deeply and diffusely. Cells with irregular nuclei and intensely oxyphil cytoplasm (recalling the polynuclear leuco-cytes) are often scattered through the stroma or are collected into more or less definite foci at the periphery of the organ.

Stomach and Intestines.

The gastric mucosa consists of a wide tubular gland system with a polyhedral investing epithelium on the free surface. The investing epithelium is regular and the cytoplasm is generally hyaline and non-granular, the nuclei are oval, sharply defined, and show a little dust-like chromatin. In the cells of the tubular glands the cytoplasm is oxyphil, the nuclei are large, round or oval, stain moderately deeply, and show a little particulate chromatin. Very few goblet cells are seen, but much mucus may be present. The intestinal mucosa is villous, the cytoplasm is hyaline, the nuclei are regular in shape, but stain very faintly and are ill-defined. The tissue sometimes looks parboiled. The stroma is myxomatous, the nuclei stain deeply and are irregular in shape.

Generative System.

The ovary consists of many lobes surrounded by a good endothelial layer and containing large quantities of spore-like bodies of varying size. The testicle shows little contraction. The seminal tubules are surrounded by a basal layer of cells very faintly stained, much broken down, and showing some large oval and some small round nuclei. Internal to this are numerous fan-shaped arrangements of intensely basophil spermatozoal heads, the pivot of which appears to dip into a basal cell and is faintly oxyphil. The middle of the tubule shows oxyphil, granular material which probably represents spermatozoal tails. The stroma is a scanty, loose, vascular, connective tissue with few cells.

Lung.

The alveolar walls are thick and frequently show unstriped muscle. They are covered by dilated capillaries with a super-ficial well-marked endothelium, of which the nuclei vary much in shape, and staining is faint. Black pigment masses are common. The alveolar spaces are empty except that they may be the seat of an animal parasite. In the bronchi the epithelium is columnar, and sometimes cilia are recognized. The nuclei vary in shape, stain moderately deeply, and show a small amount of particulate chromatin. A few goblet cells may be seen.

The Frog exposed to Radium.

The experiments upon frogs extend over so large a range of exposure that grouping is necessary. It has been thought best to divide them into (A) those animals which were exposed for less than one day, and (B) animals exposed for periods between two and five.days. In Group A, it is also possible to contrast immediate and later effects of the irradiation.

A. *Frogs subjected to a continuous exposure of less than one day.*

The animals considered in this section are as follows :

Number.	Length of exposure.	Subsequent history.	
Q 1	3 hours	Killed immediately	
Q 2	3 ,,	,,	3 days later
Q 3	6 ,,	,,	immediately
Q 7	6 ,,	,,	4 days later
Q 4	21 ,,	,,	immediately
Q 6	21 ,,	,,	3 days later

Blood.

(1) Animals killed immediately after exposure.

In the 3-hours' specimen the shape and staining of erythrocytes is good, but no leucocytes nor free nuclei are seen. In the 6-hours' specimen the shape is good, but nuclei are barely stained when viewed on the flat, though in profile, staining is fair ; no leucocytes nor free nuclei are seen. In the 21-hours' specimen shape and staining of erythrocytes vary, but may be good ; some free nuclei are seen ; the vessels may contain thrombus.

(2) Animals living 3-4 days after exposure.

In the 3-hours' specimen shape and staining are good, some free nuclei are seen, thrombus is present in some of the vessels. In the 6-hours' specimen shape and staining are variable ; no leucocytes nor free nuclei are present. In the 21-hours' specimen the erythrocytes are very irregular in shape, the nuclei are practically unstained, no leucocytes nor free nuclei are seen.

Conclusion. Leucocytes and free nuclei disappear early, nuclear staining of erythrocytes is impaired fairly early, alteration in the shape of erythrocytes and thrombosis occur later. The changes are progressive after cessation of exposure.

Striated Muscle.

(1) Animals killed immediately after exposure.

In 3-hours' specimen the contractile tissue shows fair striation (fair also in frozen sections), is fibrillar, but shows a little translucency : nuclei stain fairly. In the 6-hours' specimen striation is good (good also in frozen sections), the contractile material is fibrillar, but somewhat translucent ; the nuclei are pale, but show particulate chromatin. In the 21-hours' specimen there is no striation (good in frozen sections), no translucency, but fibriliation is present ; nuclei are faintly stained and show particulate chromatin. Lipoid is doubtfully present. The nuclei are 6-7 times as long as broad.

(2) Animals living 3–4 days after exposure.

In the 3-hours' specimen the contractile material shows slight striation (fair in frozen sections), translucency, and fibrillation ; the nuclei vary in shape and staining. There is a slight deposit of lipoid. In the 6-hours' specimen there is fibrillation, but no striation (good in frozen sections) nor translucency, and the contractile material may be oxyphil or basophil ; the nuclei vary in intensity of staining and vesicular forms are present. In the 21-hours' specimen there is a little fibrillation and translucency and striation is fair or good (good in frozen sections) ; the nuclei vary in staining and may be vesicular. There is no lipoid, but the fibres stain deeply. Between the muscle bundles is a small amount of amorphous granular material.

Conclusion. The contractile material is always fibrillar and generally somewhat translucent. Striation is better marked in frozen than in embedded specimens. No difference in striation is observed in frozen sections as the exposure is increased nor in survival animals, but 21-hours' exposure or survival after exposure is accompanied by deep staining of fibres with Sudan or by fine lipoid deposit. In paraffin sections 21-hours' exposure or survival after exposure is accompanied by deficiency or complete absence of striation. The nuclei stain more faintly and show particulate chromatin as the length of exposure increases and become variable in shape and staining when the animal survives. If the survival follow a somewhat long exposure, vesicular nuclei are observed and albuminous material may be present in dilated intermuscular spaces.

Unstriated muscle.

(1) Animals killed immediately after exposure.

In stomach the contractile material is hyaline, occasionally fibrillar and markedly vacuolated : the nuclei are thin, variable or contracted as the exposure increases, and stain relatively deeply. In intestine contractile material is hyaline, basophil, occasionally translucent, and somewhat vacuolated. The nuclei are vacuolated, faintly stained, and show dust-like chromatin at 3 and 6 hours and are vacuolated, contracted, and stain rather deeply at 21 hours. In lung the contractile material is usually fibrillar and hyaline but much vacuolated, the nuclei stain moderately throughout, but are irregular and vacuolated as the exposure increases. In artery the contractile material may be hyaline or fibrillar, but is usually vacuolated to a moderate degree ; the nuclei vary much in shape and staining.

(2) Animals living 3–4 days after exposure.

In stomach the contractile material is somewhat translucent and highly vacuolated ; the nuclei are faintly stained rods at 3 and 6 hours, contracted and deeply stained at 21 hours. In intestine the contractile material is hyaline and much vacuolated, especially after longer exposures, but may be translucent or fibrillated ; the nuclei are irregular and stain faintly. In lung the contractile material is hyaline or definitely translucent and somewhat vacuolated ; the nuclei are contracted, may be vacuolated

and stain faintly. In artery the contractile material is hyaline or fibrillar and somewhat vacuolated ; the nuclei are irregular, deeply stained, and may be vacuolated.

Conclusion. Vacuolation is pronounced in the contractile material and often present in nuclei. It is not more marked in survival animals. Translucency is present in animals that have survived. The nuclei tend to become contracted and to stain deeply as the exposure is longer and contraction is more marked in survival animals. The intermuscular spaces are moderately wide and contain no adventitious cells or materials.

Cardiac Muscle.

(1) Animals killed immediately after exposure.

In the contractile material there is moderate fibrillation. The fibres are finely granular in the 3 and 6 hours' specimens, but striation is only seen in the 3-hours' specimen. With an exposure of 21 hours, the contractile material is hyaline and vacuolated. The nuclei are rods about six times as long as broad, but are more variable and perhaps shorter with the 21-hours' exposure. Staining is moderate and chromatin is particulate in the 3-hours' specimen, it is faint and dust-like in the 6 and 21 hours' specimens.

(2) Animals living 3–4 days after exposure.

The contractile material is moderately fibrillated and may be granular, but there is no striation. The nuclei vary in length and thickness ; staining is moderate and chromatin is particulate at 3 hours, faint and dust-like at 6 hours, moderate and diffuse at 21 hours. A little albuminous material may be found in the intermuscular spaces.

Conclusion. Striation is rarely found but the fibres are finely granular or may be hyaline. The nuclei tend to show fainter staining and dust-like chromatin or even diffuse staining as the exposure is lengthened. The intermuscular spaces are wide and in survival animals may shew a little coagulated albumin.

Connective Tissue.

(1) Animals killed immediately after exposure.

There is a delicate fibrillar, sharply defined meshwork in the 3-hours' specimen which is loose and oedematous in the 6 and 21-hours' specimens. Few nuclei are seen.

(2) Animals living 3–4 days after exposure.

At 3 and 6 hours there is a sharply defined, delicate, fibrillar meshwork with a few small, contracted, deeply stained nuclei. At 21 hours the nuclei are similar, but the stroma is myxomatous.

Conclusion. With lengthened exposure or with survival animals the connective tissue becomes oedematous or myxomatous, and the nuclei become contracted and deeply stained.

Endothelium.

(1) Animals killed immediately after exposure.

Over stomach at 3 and 6 hours, the layer is fair, the nuclei round or oval, moderately stained. At 21 hours it is detached and

degenerated, and the nuclear shape and staining are irregular. Over intestine the layer is poor in all specimens, the nuclei vesicular or deeply stained or irregular. Over spleen, lung, heart, testicle, ovary, the layer is fair, but at 21 hours is detached and degenerate. The nuclei are irregular in shape, staining is fainter as the exposure increases. In artery endothelium is fair, the nuclei vary in shape but stain faintly.

(2) Animals living 3–4 days after exposure.

Over stomach the layer is detached and the nuclei are ill-defined or irregular and stain moderately or deeply. Over intestine it is largely detached and the nuclei stain deeply. Over spleen, lung, heart, testicle, ovary the layer is detached or fragmented or degenerated, and the nuclei are very irregular in shape and stain faintly. In artery a moderate endothelium is present and the nuclei vary in size and depth of staining.

Conclusion. Endothelium is most affected over intestine, within blood-vessels it is least affected. In the other regions examined, detachment occurs as exposure is lengthened or follows on survival. With longer exposures detachment is associated with degeneration and with irregularity in shape and faint staining of nuclei.

Liver.

(1) Animals killed immediately after exposure.

The tissue is coherent, the blood-vessels dilated and contain thrombus, but few corpuscles are seen. The hepatic cells are polygonal and the outlines are sharply defined. The cytoplasm is finely granular, scanty in the 3 and 6 hours', very scanty in 21-hours' specimen and tends to accumulate close to the partition between adjacent cells. Staining of the granules is oxyphil and fairly good. The nuclei are round, even in size and show particulate chromatin. As length of exposure increases nuclear staining diminishes in intensity. 'Ghosts' occur and cells are found in which no trace of nucleus is visible. Bile ducts are lined by a homogeneous epithelium but become filled with coagulum and ultimately invisible as the exposure lengthens. Black pigment is scattered through the tissue in fair quantity. No lipoid is found.

(2) Animals living 3–4 days after exposure.

In the 3 and 6 hours' specimens cell outline is good, but at 21 hours the cell membrane is much broken. Cytoplasm is scanty or very scanty, finely granular, often collected close to the partition between adjacent cells. In all the specimens nuclei may lie in clear spaces, and from many cells they have disappeared entirely. 'Ghosts' are numerous. Well defined nuclei are round, even in size, sharply defined, faintly stained, and show a little particulate chromatin. Bile ducts are lined by a degenerated epithelium or are not recognizable. A great quantity of black pigment is present in the 21-hours' specimen. No lipoid is found.

Conclusion. Hepatic changes are pronounced and progressive both as regards length of exposure and survival after exposure

Cytoplasm appears to show effects earliest and ultimately disappears almost entirely. The nuclear chromatin stains less intensely and becomes scanty as exposure is lengthened or survival occurs until it ultimately disappears through intermediate stages of ghost-like forms and small constellations of chromatin without nuclear membrane. Bile ducts appear liable to be occluded with coagulum and, with lengthened exposure, to become unrecognizable.

Spleen.

(1) Animals killed immediately after exposure.

The number of cells present is diminished, and, as exposure lengthens, erythrocytes tend to predominate considerably and non-haemal cells disappear. Traces of Malpighian corpuscles or germinal areas are found in all cases. The non-haemal cells appear to be endothelial alone, but the nuclei show a progressive irregularity in shape and increased depth of staining as the exposure lengthens. As diminution in number of cells proceeds a fine stroma becomes evident. There is no nuclear débris nor is pigment present.

(2) Animals living 3–4 days after exposure.

The diminution in number of endothelial cells is more marked, their nuclei become more irregular in shape and staining, stroma is more evident, the erythrocytes come into prominence and may form irregular, conglomerate masses. Malpighian corpuscles may be unrecognizable. There is no nuclear débris nor pigment.

Conclusion. The non-haemal cells disappear in large numbers and those remaining are endothelial cells with damaged nuclei. Hence stroma and erythrocytes come into view. Blood changes may be observed, but there is no nuclear débris. Survival after exposure is associated with some intensification of the changes.

Pancreas.

(1) Animals killed immediately after exposure.

The structure is acinous and appears better preserved as exposure lengthens. The cytoplasm of a 3-hours' specimen is contracted and vacuolated and the nuclei are irregular. of a 21-hours' specimen. cytoplasm is granular and nuclei are round and moderately stained. In the acini the nuclei are peripheral and that part of the cytoplasm is usually basophil, the central portion being faintly oxyphil. It is very doubtful whether islands of Langerhans are represented.

(2) Animal living 3–4 days after exposure.

Only 21-hours' specimen is available. It shows good general structure. granular basophil cytoplasm and irregular. deeply stained nuclei.

Conclusion. General structure is better as the exposure is lengthened. but nuclear staining tends to become deeper.

Kidney.

(1) Animals killed immediately after exposure.

The glomerular tufts are a little contracted and show no albumin in the 3-hours' specimen. but at 6 hours some are contracted. others

are swollen and show a little coagulated albumin, and at 21 hours the entire tuft may be replaced by coagulated albumin. The capillary vessels of the tuft are widely dilated but often show few corpuscles. The endothelial cells covering the tuft show an increasing irregularity in shape and depth of staining as exposure lengthens. The endothelium lining Bowman's capsule degenerates and disappears as the exposure lengthens and the amount of coagulated albumin in the glomerular space increases. Red blood corpuscles are not found in the glomerular space. In the convoluted tubules the lumen is wide and contains amorphous, albuminous material, the cytoplasm of the renal cells is broken down or scanty or vacuolated, the nuclei are irregular in shape, vacuolated, contain little chromatin, may be nucleolated and 'ghosts' are present. The nuclei may lie in a central space. These features increase as the exposure lengthens. In conducting tubules the appearances are similar to those in the convoluted tubules but less pronounced. The blood supply of the organ is considerable but appears uninfluenced by duration of exposure. The stroma is scanty and the connective tissue nuclei stain well. Cells with irregular, deeply stained nuclei and intensely oxyphil, non-granular cytoplasm are seen in small numbers scattered through the stroma in 3 and 6 hours' specimens, and in considerable numbers in the 21-hours' specimen.

(2) Animals living 3–4 days after exposure.

The glomerular tuft is sometimes contracted, sometimes contains albuminous deposit, but the capillaries, when present, are widely dilated. As the exposure lengthens the amount of albumin increases, and in the 21-hours' specimen, albuminous deposit completely obscures many of the tufts. The nuclei covering the tuft become more irregular in shape and deeper in staining as exposure lengthens. The endothelium lining Bowman's capsule usually persists in a debased form and the glomerular space contains albuminous material without admixture of red blood corpuscles. In the convoluted tubules the lumen is wide and contains granular or albuminous material. The cytoplasm of the renal cells is broken down or granular or vacuolated, the nuclei sometimes stain deeply, but usually are faintly stained, present a little particulate chromatin, and may lie in a central clear space. 'Ghosts' are present, and in the 21-hours' specimen 'ghosts', vacuolation, and complete disappearance of nuclei are common. In conducting tubules the lumen is wide and contains granular material in varying degree. The cytoplasm of the cells is hyaline (3 hours), granular (6 hours), granular and vacuolated (21 hours); the nuclei are irregular, stain more faintly with longer exposures and may be vacuolated. 'Ghosts' are present. The conditions are more pronounced as exposure is longer. The blood supply of the organ is not great. The stroma is scanty and shows considerable numbers of cells with deeply stained, irregular nuclei and intensely oxyphil, non-granular cytoplasm. These cells are usually collected in foci of some size.

Conclusion. The glomeruli show an increasing damage to the capillaries which is sufficient to allow exudation of plasma, but

does not permit corpuscles to pass. This is associated with a modification of the endothelial cells in the glomerulus. In the convoluted tubules casts of albuminous or granular material are found. The cytoplasm of the renal cells is broken down, the nuclei tend to stain either unusually deeply or unusually faintly and may become vacuolated. 'Ghosts' are numerous and actual disappearance of nuclei occurs. In conducting tubules similar appearances are met with but are less marked. The changes mentioned above are associated with a diminishing vascularity of the organ and an increasing infiltration of the stroma with cells recalling the polynuclear leucocytes of mammalian blood. As the duration of exposure is increased or survival occurs the features in question become intensified.

Stomach and Intestines.

(1) Animals killed immediately after exposure.

In stomach there is a mucosa covered by an investing epithelium and presenting short, wide tubular glands. The cells of the investing epithelium are polyhedral and moderately defined, the cytoplasm is broken (3 hours), vacuolated (6 hours), mucoid (21 hours); the nuclei vary but generally stain faintly and show little chromatin. In the tubular glands the lumen is wide; the cytoplasm of the lining cells is scanty but may be swollen and vacuolated; the nuclei are faintly stained, irregular in shape, and with longer exposures, are swollen or vesicular. The intestinal mucosa is villous, well defined (3 and 6 hours), cloudy (21 hours), and covered with a fair investing epithelium between the mouths of the tubular glands. In the 21-hours' specimen the mucosa of the lower intestine is detached and degenerated. The cytoplasm of the cells generally is vacuolated; the nuclei are nucleolated, often vacuolated or vesicular (21 hours), staining varies in depth and little chromatin is seen. The stroma is scanty, oedematous, and provided with few, moderately deeply staining, irregular nuclei.

(2) Animals living 3–4 days after exposure.

In stomach the investing epithelium is fairly preserved but the cytoplasm of the cells is shrunken, or mucoid, or broken, and the nuclei may be swollen and moderately stained, or (21 hours) contracted and deeply stained. In the tubular glands the epithelium is more or less broken up and degenerated, the nuclei are irregular in shape and staining, show little chromatin, may be nucleolated or are vesicular. There is definite formation of mucus. In intestine, the villous mucosa is usually cloudy. The cytoplasm of the cells is vacuolated, the nuclei swollen, faintly stained, and perhaps nucleolated. Goblet cells are present and their numbers increase with length of exposure, free mucus may be found in the lumen of the gut. The stroma is scanty and oedematous, and in the 21-hours' specimen shows some small mononuclear cells.

Conclusion. The mucosa of stomach is less affected than that of intestine, but in both situations degeneration and disintegration occur. With shorter exposures, the chief changes are swelling

and vacuolation of cytoplasm and feeble nuclear staining. With longer exposure and in surviving animals, mucoid change becomes pronounced and there may be desquamation. The stroma is oedematous in all cases.

Generative System.

No certain differences can be seen in the testicle between animals killed immediately after exposure or those surviving 3–4 days, nor is a difference found between short and long exposures. It is possible that staining of spermatozoal heads is not so intensely basophil with longer exposures and that degeneration and faint staining of the basal layer of cells in the tubule are more pronounced. No ovary is included in this series.

Lung.

(1) Animals killed immediately after exposure.

The alveolar walls show wide capillaries and an endothelium in which the nuclei are round or oval and moderately stained. The alveolar space shows a small amount of débris or a few red blood corpuscles. The bronchi are lined by a columnar epithelium with poor ciliation, round or oval, moderately staining nuclei and some goblet cells. In the 21-hours' specimen there is disintegration of epithelium. Pigment is present to a greater extent in the 21-hours' specimen. All 3 animals bore animal parasites.

(2) Animals living 3–4 days after exposure.

In the alveolar walls the capillaries are wide, may show corpuscles and the endothelial nuclei are irregular in shape and stain deeply. The alveolar space shows red corpuscles, albumin, or débris. Ciliation in the bronchi is poor and the epithelium is disintegrated in the 21-hours' specimen. The nuclei stain rather faintly, goblet cells are present, and there is definite mucus formation. The amount of pigment increases with the duration of exposure.

Conclusion. In the alveolar walls irregular shape and deep staining of endothelial nuclei occur and the alveolar spaces show red blood corpuscles or débris increasing in amount with survival. The columnar lining of the bronchi shows goblet cell formation, tendency to loss of cilia and disintegration; these increase with survival and are particularly noticeable in the 21-hours' specimen.

B. *Frogs subjected to a continuous exposure varying from 2 to 5 days.*

The animals considered in this section are as follows : it will be noticed that all except two were allowed to die.

Number.	Length of exposure.	Subsequent history.
Q 5	45 hours	Killed immediately
Q 9	64 ,,	Died under radium
Q 10	64 ,,	ditto
Q 11	80 ,,	ditto
Q 8	96 ,,	Killed 3 days later
Q 15	108 ,,	Died 2 days later
Q 16	108 ,,	,, 5 ,, ,,
Q 13	112 ,,	,, 5 ,, ,,
Q 17	125 ,,	,, 7 ,, ,,
Q 12	128 ,,	,, shortly
Q 14	128 ,,	,, 2 days later

Macroscopically no abnormality is observed in most cases, but there may be dryness of skin and redness of digits, and with more prolonged exposure, distension of stomach and haemorrhage into intestine.

Blood.

The shape of red blood corpuscles is long preserved and the first abnormality consists in poor nuclear staining. This is followed by partial disintegration of corpuscles and, still later, by deposition of fibrin. In the longest exposures the red blood corpuscles are very irregular in shape, fragmented, and stain poorly, the nuclei are very pale or are unrecognizable, and there is considerable deposition of fibrin in the organs. Degenerative changes appear to occur earliest in spleen and liver. No leucocytes are seen through the whole series, but free nuclei are occasionally present.

Striated Muscle.

Striation is better in frozen sections than in those that have passed through the paraffin process, but on the whole the two series run parallel. Striation is very poor or lost even in frozen sections when the exposure has been 4 days or longer. Translucency of fibres is generally present but appears to be less marked with longer exposures when the fibres are broken and granular. The greatest manifestation of lipoid is in the middle of the series, under shorter or longer exposures there is a diffuse staining of the fibres, but globules of lipoid are not seen. Striation tends to be worse and translucency to be more marked in adductor muscle than in gastrocnemius. Gastrocnemius is oxyphil but adductor is less oxyphil or definitely basophil. The muscle nuclei vary much in shape and depth of staining. Vacuolated or vesicular forms are always present and become more numerous as exposure is increased, but actual 'ghosts' are few. The chromatin is generally scanty and particulate in well preserved nuclei and swelling is usual, length being roughly 4–5 times the breadth. The intermuscular space varies in width, is generally empty, but may contain a little albuminous deposit.

Unstriated Muscle.

In stomach great vacuolation of contractile material is common, and with prolonged exposures the muscle is so much broken up that fragments of contractile material lie in large clear spaces. Such contractile material as persists is hyaline. The nuclei are contracted or irregular in shape, frequently vacuolated or vesicular, and usually stain moderately or faintly and diffusely. In intestine vacuolation is also seen in the contractile material, but is not so great as in stomach. On the other hand, the tissue is more broken up in intestine, and with longer exposures much of the contractile material has disappeared. The nuclei are irregular or contracted, often vacuolated and stain deeply. With longer exposures the intermuscular spaces in both stomach and intestine are widened and contain a mucoid or gelatinous material. In lung the contractile material is voluminous and hyaline, but may

show some fibrillation. Vacuoles and clefts occur but are not a pronounced feature. The nuclei are contorted or contracted, and vary much in depth of staining; frequently they show some vacuolation. In artery the appearances differ somewhat according to size of the vessel. In large vessels there is a tendency for the contractile material to be cloudy or gelatinous or to stain poorly. It is generally hyaline, but occasionally fibrillation is good. Clefts and vacuoles may be found but are absent with extreme exposures. This is not because the disintegration is great as in stomach and intestine. The nuclei are contorted or irregular in shape, may stain faintly or deeply and occasionally are vacuolated. In arterioles the chief difference lies in the absence of vacuolation.

Cardiac Muscle.

The tissue is generally fibrillar and sometimes markedly so. The fibrils are usually finely granular, rarely hyaline. No striation is seen. Fragmentation may occur and, with lengthy exposures, the tissue is cloudy; vacuolation is not uncommon. The nuclei vary much in shape, ratio of length to breadth and staining, and may be vacuolated or vesicular. They rarely show more than a little dust-like chromatin. The interfibrillar and intermuscular spaces are wide and may contain red blood corpuscles or, with extreme exposures, plugs of fibrin.

Connective Tissue.

The fibrils are delicate but, as exposures lengthen, become swollen, though very rarely granular. The interfibrillar material increases and the tissue becomes gelatinous or myxomatous in character. The only cells present are a few endothelial and connective tissue cells.

Endothelium.

Over stomach the endothelium is more or less detached and may be present in traces only. The nuclei are irregular in shape and staining. Over intestine the condition is worse, detachment and fragmentation being the rule and few nuclei being seen, and those being contracted and deeply stained or sometimes vesicular. Over spleen, lung, heart, and testicle or ovary, traces alone are usually seen with ill-defined, pale nuclei and granular cytoplasm. Within the blood-vessels the endothelium is better than elsewhere. The layer is generally attached and the nuclei, when seen in profile, are linear and stain deeply. With lengthened exposures, the nuclei stain faintly and are vesicular, and the endothelium may be difficult to distinguish.

Liver.

The blood-vessels, including the capillaries, are widely dilated and usually contain many red blood corpuscles. Over the latter half of the series the red blood corpuscles show signs of disintegration and fibrinous plugs are seen. Similarly cohesion of the liver tissue is impaired and the cells become separated from one another. The hepatic cells are polyhedral and contain a granular

cytoplasm which varies in amount but frequently is scanty and confined to a few granules collected close to the partition between adjacent cells. The cell membrane is usually distinct, but with the more prolonged exposure it is broken down or ill-defined. The nuclei are small, round, even in size, sharply defined, contain a little particulate chromatin and perhaps a nucleolus; owing to scantiness of cytoplasm they often lie in a clear space. 'Ghosts' are always present and sometimes in great numbers. Cells without nucleus occur and sometimes the nuclei are vesicular, but small constellations of chromatin without nuclear membrane are not seen. Focal degeneration of liver tissue into an amorphous granular material is met with under the more lengthened exposures. The bile ducts are not always detectable, but when present, show a swollen, low columnar epithelium with vesicular, very faintly stained nuclei. The lumen is always small and may be occluded with a plug of fibrin. Pigment occurs as irregular black masses of moderate size. It is found in all cases and to the greatest extent over the middle portion of the series. In frozen sections a small amount of lipoid is found in some of the specimens but no relation to length of exposure can be detected.

Spleen.

The tissue is relatively acellular with more prolonged exposures and only occasionally yields appearances suggestive of Malpighian corpuscles. Haemal and non-haemal cells may be present in equal numbers or the haemal cells may predominate. In the latter case they may be accumulated into irregular masses and corpuscular fragmentation is common. The nuclei of non-haemal cells vary widely in appearance but usually are large, faintly stained, and may be vesicular. Occasionally deeply stained, free nuclei, and a few young red blood corpuscles are seen and, with longer exposures, there is a fair amount of nuclear débris and foci of fibrinous deposit are present. The stroma comes into view as acellularity is more marked. It is little fibrillar and in the main homogeneous or vacuolated and finely granular. Little pigment is seen but when present it may be haematogenous or non-haematogenous and usually is extracellular. The mean amount of spleen is 0·072 cc. per cm. of length.

Pancreas.

There is a low order of acinous arrangement or the cells may be separated. The cytoplasm is hyaline or cloudy and oxyphil at the centre of the acinus but basophil peripherally in the nuclear region. The nuclei are irregular in shape and stain deeply but may be vesicular. The ducts are lined by a low columnar epithelium with conglomerate hyaline cytoplasm and swollen, vesicular nuclei which are moderately stained and probably nucleolated. Islands of Langerhans are not seen.

Kidney.

The glomeruli show an increasing series of changes as exposure lengthens, but not all glomeruli in a single kidney are in

the same state. In earlier members of the series the tuft may be contracted or cloudy, will show widely dilated capillaries and fair numbers of round or oval, moderately stained endothelial nuclei. The endothelium lining Bowman's capsule varies but is fairly good and the nuclei stain well. The glomerular space is empty. With longer exposures there is local deposition of fibrin in the glomerular vessels and patent capillaries are few though widely dilated and full of corpuscles. The endothelial nuclei covering the tuft are irregular in shape or fragmented and deeply stained. Definite haemorrhage occurs but is rare. The endothelium lining Bowman's capsule is degenerated and stains poorly, the glomerular space may contain traces of albuminous débris or a few red blood corpuscles but usually is empty. In the convoluted tubules the lumen is usually very small and may be bridged by strands of albumin derived from disintegration of cytoplasm or blocked by albuminous casts or, with longer exposures, by the entire ring of epithelium which has become detached and is undergoing degeneration. The cytoplasm of the renal cells may be hyaline, vacuolated or granular, but in the majority of cases, is breaking down. The nuclei are round, faintly stained, and show a little particulate chromatin when in a relatively good state of preservation. On the other hand 'ghosts' and small constellations of chromatin without nuclear membrane and regions of cytoplasm without evidence of nucleus are frequent. Over the latter half of the series these degenerated nuclear forms predominate. In the conducting tubules (not always easy to distinguish from convoluted tubules) the appearances are similar but the tubules are smaller and there is not the same tendency to obstruction of the lumen or disintegration of cells. The nuclei stain faintly and are vesicular. The stroma of the organ is scanty, but in many cases, contains cells with irregular, deeply basophil nuclei and intensely oxyphil, nongranular cytoplasm. These cells, which recall polynuclear leucocytes in some respects may be scattered widecast or collected into more or less definite foci. The blood-vessels are dilated but may contain few red blood corpuscles. Occasionally foci of fibrinous deposit are present.

Stomach and Intestines.

The gastric mucosa shows a system of short wide tubules set in a delicate connective tissue and covered superficially by a polygonal epithelium. But the cytoplasm of the cells in the tubular glands tends to disappear, the connective tissue becomes gelatinous and swells and the superficial epithelium undergoes mucoid degeneration and desquamation. These changes increase as the exposure lengthens and over the latter half of the series the secreting elements have become converted into mucus or have desquamated or have disappeared entirely and the mucosa comes to consist of little more than a gelatinous villous connective tissue with some traces of investing epithelium. Concurrent with the changes in cytoplasm the nuclei have swollen enormously and become vesicular, but in the last stages, such

nuclei as remain are contracted and deeply stained. In intestine the mucosa is villous, cloudy, and shows vacuolated or vesicular, faintly stained nuclei in the first half of the series, but is much degenerated, is practically converted into mucus and has desquamated in the latter half of the series. The stroma is always more conspicuous and less changed than is the secreting epithelium. It is fibrillated, but as exposures lengthen, it becomes more and more gelatinous and swollen and the lymphatic channels are enormously dilated. A few contracted, deeply stained connective tissue nuclei and swollen, faintly stained endothelial nuclei are the sole varieties found.

Generative System.

No certain difference from the normal obtains in either testicle or ovary. It is possible that there is greater disorganization of the basal layer of cells in the seminal tubule and, with extreme exposures, the fan-shaped masses of spermatozoal heads appear to be broken up in some degree. The spermatozoal heads show no greater change in staining reaction than a tendency to stain more faintly than usual and to be of a purple or mauve tint with haematoxylin rather than intense blue.

Lung.

The alveolar walls are thick and show widely-dilated superficial capillaries which may be blocked up with fibrin. The endothelial cells vary much in shape and staining, the nuclei being usually deeply stained and contracted but sometimes vesicular. The alveolar space nearly always contains a small amount of granular albuminous material sometimes mixed with red blood corpuscles or mucus. In the bronchi the lining columnar epithelium may be fairly adherent or desquamated and degenerated, the latter condition being most marked with longer exposures. The cells of a relatively well-preserved layer may be ciliated and show many swollen goblet cells, little free mucus within the lumen of the tube, or the cilia may have disappeared and then a considerable formation of mucus is usual. The nuclei of the columnar cells generally stain faintly and may be vesicular. The majority of animals in this series showed animal parasites in the lung. A small to moderate amount of black pigment is present in irregular masses and lies in the subvascular tissue of the alveolar walls.

HISTOLOGICAL CHANGES IN THE RAT

The Normal Rat

Blood.

Within the vessels the red blood corpuscles are sometimes discrete but may be merged into a coherent mass. Staining is moderate. Leucocytes are always found and usually lymphocytes predominate largely. Nuclear staining is intensely basophil. There is no thrombosis of vessels.

Striated Muscle.

The appearances vary not only as between muscles from different sites (abdominal, thoracic, biceps) but also as between specimens of the same muscle. Striation is always found in some fibres but may be good or poor. Irregularly contorted and translucent fibres in which striation is usually absent may be placed in close proximity to others in which the outlines are parallel, the fibres lie flat and striation is good. Uneven staining of a section is common but there is no superficial stained albuminous deposit. The contractile material is usually hyaline but may be granular or translucent. The fibres are fairly distinct. The nuclei are fusiform or oval and show a little dust-like or particulate chromatin on a pale diffuse basis. When viewed from abnormal points the nuclei may be deeply stained. The abdominal muscle nuclei are about $5\frac{1}{2}$ times as long as broad, bicipital nuclei about 3 times as long as broad. The intermuscular spaces are small and contain no adventitious material. In frozen sections stained with Sudan or scarlet, striation is very good and there is no lipoid deposit. The fibres take very little stain.

Unstriated Muscle.

The contractile material is hyaline but gives evidence of fibrillation. In the stomach a certain degree of fenestration or vacuolation is present and, in the transversely-cut external coat of intestine, the individual bundles are often separated or broken up and may show vacuolation though to a less extent than the gastric muscle. The nuclei are long rods, sometimes wavy or fusiform or with irregular outlines, usually staining faintly and diffusely but showing a little particulate or dust-like chromatin. There is no evidence of vacuolation or vesiculation and no ' ghosts ' are present. The intermuscular spaces are small and contain no adventitious material. In artery the contractile material tends to be hyaline, is not vacuolated, and shows great irregularity in shape of its faintly staining nuclei.

Cardiac Muscle.

The contractile material is hyaline, fibrillated, rarely granular, and shows striation in some fibres though such striation is poor. It is not translucent. The nuclei are rods with square ends about 5 times as long as broad and show a little particulate chromatin upon a pale diffuse basis. The intermuscular spaces are small and contain no adventitious material.

Connective Tissue.

The dense variety shows narrow, somewhat translucent fibrils with intervening linear or contracted, deeply stained nuclei. The loose variety shows a fine meshwork of sharply defined delicate fibrils, without granularity. The nuclei are few, contracted and deeply stained but some pale, oval, diffusely stained endothelial nuclei may be enclosed in the meshwork.

Endothelium.

Over stomach there is a good layer of attached endothelium in which the nuclei are placed rather close together. The nuclei

are linear and deeply stained if viewed in profile, faintly and diffusely stained if viewed on the flat. Over duodenum the layer is broken or partially desquamated and the nuclei are contracted or vesicular and vary in depth of staining. Over jejunum and ileum the layer is generally better preserved than over duodenum, but, over colon, it is again liable to be broken or partially desquamated; over rectum it varies but sometimes is good. The nuclei vary in shape and staining accordingly. Where the layer is good they are linear and deeply stained in profile and round or oval, moderately and diffusely stained when viewed on the flat. Where the layer is disintegrating, variably stained, vesicular or irregular nuclei are present and cytoplasm is barely represented. In blood-vessels the endothelium is well preserved. In veins the nuclei are linear, but in arteries, owing to muscular contraction they are irregular in shape. In both instances staining is deep and diffuse. Desquamation is rare and only found in great vessels. Over spleen the endothelium is well preserved, regular, formed by a single layer of cells and the nuclei are linear and deeply stained as a rule. In the spleen pulp the nuclei are large, round or oval, faintly stained, show a little particulate chromatin, and are apparently surrounded by little cytoplasm, but the cell outlines are rarely visible. In lung the endothelial nuclei of the alveolar walls are round or varied in shape, smaller than elsewhere, and generally stain deeply and diffusely.

Liver.

The tissue is somewhat loosely coherent and shows widely dilated blood-vessels and capillaries. The number of red blood corpuscles present varies. The hepatic cells show a large amount of coarsely granular cytoplasm and the partitions between adjoining cells are ill-defined or not visible. There is no vacuolation or fat lacunae. The nuclei are round, even in size, well-defined, usually nucleolated, moderately stained, and show a small amount of particulate chromatin. No 'ghosts' or otherwise degenerated nuclei are seen. Scattered through the tissue are isolated, deeply stained, small, lenticular nuclei without obvious cytoplasm. These are often attached to the capillary wall, but it is doubtful whether they are endothelial. The stroma is scanty and little cellular. The bile ducts may be inconspicuous. They show a single layer of low columnar cells with continuous cytoplasm and nuclei that contain very little chromatin and may be vesicular. Frozen sections stained with Sudan vary in respect of the presence of lipoid but usually little is seen.

Spleen.

The mean amount of spleen per cm. of length of the animal is 0.085 c.c. Malpighian corpuscles are always seen but may be many or few. The tissue varies in degree of cellularity but usually is highly cellular and shows a predominating number of red blood corpuscles. Lymphocytes with deeply stained, small, round nuclei and no visible cytoplasm are the chief nucleated

cell present and constitute the bulk of cells in the Malpighian corpuscles. In the intervening spleen pulp there are some large, round or oval faintly stained nuclei of endothelial cells, the cytoplasm of which is hyaline, scanty, and conglomerate. No pigment bearing endothelial cells are seen and plasma cells are few. There is no nuclear débris. The stroma is very scanty, but a few trabeculae in which are unstriped muscle nuclei are seen.

Pancreas.

The coarse structure is well preserved but in the acini, the cells are ill-defined and sometimes partially broken up. The cytoplasm is hyaline, usually oxyphil in the centre of the acinus and basophil at the periphery where the nuclei are situated. The nuclei are round, sometimes vesicular, sometimes deeply stained but usually are ill-defined.

Kidney.

The glomerular tufts are usually a little shrunken and show few patent capillaries and few red blood corpuscles. The endothelial nuclei of the tuft are round or oval or slightly irregular in shape and deeply stained. Those lining Bowman's capsule form a regular layer, are few in number, linear, and deeply stained. The glomerular space is generally empty but occasionally may contain a single red blood corpuscle or a trace of albuminous material. The convoluted tubules present an irregular lumen which varies in width according to the degree of disintegration of the internal part of the renal cells. Such partial disintegration leads to the formation of irregular albuminous débris or ' bridges ' and is always present to some degree, but the lumen may be small or large. The tubule in cross-section is lined by a layer of 5–6 irregularly cuboidal cells with slightly granular cytoplasm of which that part which lies next the basement membrane shows traces of radial striation. The nuclei are round, even in size, faintly stained, show a small amount of particulate or dust-like chromatin, may be nucleolated, owing to disintegration of cytoplasm they may abut on the lumen. ' Ghosts ', vesicular and vacuolated nuclei are practically absent, there is no desquamation nor are casts found in the tubules. In the conducting tubules the lumen is wide and circular, usually empty but may contain a little granular débris or a few ' bridges '. The cytoplasm is scanty, hyaline or faintly granular and the nuclei are round or slightly irregular in shape, stain faintly and diffusely or a little irregularly. Definitely degenerative forms are practically absent. The large blood-vessels of the organ contain a fair amount of blood, but there is no congestion and no evidence of extravasation. The stroma is very scanty, the connective tissue cell nuclei are contracted and moderately stained and no adventitious cells are seen. The epithelium lining the pelvis is in a single cell layer over the papillae but gradually becomes converted into one composed of five or six cells irregularly disposed as the ureter is approached. The nuclei are round or oval or contracted, stain moderately or faintly, and often lie in lacunae owing to

contraction of the scanty cytoplasm. No lipoid is found in any of the renal cells.

Adrenal.

The zona glomerulosa consists of relatively small cells with little granular cytoplasm and round or oval, moderately and diffusely stained nuclei. There is a suggestion of parallel arrangement of the cells. The cortex consists of large polygonal cells with poorly-defined outlines and a finely granular or foam-like cytoplasm. The nuclei are fairly central, small, round or oval, even in size, rather faintly and diffusely stained but may show nucleoli or a trace of particulate chromatin. The cells are cloudy in appearance and usually a little broken down, but few definite fat lacunae are present. The medulla shows a coarse, spongy, finely granular network resulting from coalescence of the cytoplasm of the cells. The granules take the basic stain. The nuclei are relatively large, round or oval, usually lightly and diffusely stained and show traces of particulate chromatin or are even vesicular in character. The organ is fairly vascular and small capillaries filled with corpuscles ramify in the cortical region. Frozen sections stained with Sudan show great numbers of small, bright orange globules over the whole cortical region : very few of these are doubly refracting.

Stomach and Intestines.

The cardiac region of the stomach is lined with squamous epithelium. This consists of a somewhat ill-defined Malpighian layer succeeded by (a) two or three layers in which the cells are large, irregular in shape, hyaline and provided with a vesicular nucleus or a contracted, deeply stained nucleus lying in a lacuna, (b) a well-marked stratum granulosum in which are numbers of intensely staining eleidin granules, and (c) several keratinised layers in process of desquamation. The pyloric region shows a mucosa consisting of closely-packed tubular glands with scanty intervening stroma. In the tubules are two varieties of cells to some extent intermingled. Towards the blind end are small irregular cells with scanty basophil granular cytoplasm and small, round, moderately stained nuclei. Towards the orifice of the gland are larger and more regular polygonal cells with oxyphil, hyaline or faintly granular cytoplasm and well-defined round or vesicular nuclei. As the orifice of the gland is approached these cells desquamate and degenerate. No mucus is seen. In *duodenum* there is a voluminous villous mucosa consisting of tubular glands in which the cytoplasm is granular and continuous and the nuclei are irregularly oval in shape, closely packed, ill-defined, moderately stained and usually somewhat vesicular in character. Goblet cells are numerous but there is no accumulation of mucus in the lumen of the gut. Great numbers of mitoses are present in the cells. The stroma is considerable and contains many cells of which the majority are endothelial, small mononuclear and plasma cells. The relative proportions of these cells varies. A certain amount of desquamation of investing

epithelium is common so that the tips of the stromal prolongations between the tubular glands are denuded but they show no inflammatory or necrotic changes. In *jejunum* the appearances are similar but not so marked. The goblet cells and mitoses are fewer, the cellularity of the stroma is less and nuclei of unstriated muscle are seen, less material is found in the lumen and definition in general is better. In *ileum* the mucosa are less voluminous, mitoses are very numerous, there may be some desquamation of investing epithelium and denudation of stroma ; the stroma is less cellular but the varieties of cells present are the same as elsewhere. In *colon* the mucosa is thrown into large folds and shows tubular glands in which there are numbers of goblet cells. The cytoplasm of the cells is scanty and the nuclei are ill-defined, vary in depth of staining, and usually are compressed. Mitoses are common. As a rule there is a good investing columnar epithelium with a considerable amount of continuous hyaline cytoplasm and oval, rather faintly stained nuclei in which is a little dust-like chromatin. The main trunk of stroma is loose and the strands between tubular glands are narrow. The central lymphatic is wide. The chief cells present are endothelial and small mononuclear or lymphocytic, but they are few in number, sometimes plasma cells are seen. In *rectum* the secreting element is less represented and stroma is more voluminous. The general features are similar to those in colon, but goblet cells are more numerous and the stroma is less cellular. A good investing epithelium is usually present.

Generative System.

In the testicle the seminal tubules show some contraction of their cellular contents, but the shape is preserved. They vary in composition, but usually present a peripheral regular layer of small cells with small, round, intensely and diffusely stained nuclei (spermatogonia). Here and there amongst this peripheral layer are large cells with large oval, very faintly stained nuclei and a moderate amount of hyaline cytoplasm (cells of Sertoli). These cells are often distinguished with difficulty. Internal to the spermatogonia is a layer of large round cells with little cytoplasm and a large, moderately and diffusely stained, round nucleus (spermatocytes), and these are followed by one or two layers of similar but smaller cells with faintly stained, vesicular nuclei (degenerated spermatocytes). The centre of the tubule shows basophil spermatids or spermatozoal heads or spermatozoa together with oxyphil granular material or whorled bundles of spermatozoal tails. Sometimes four or five spermatozoal heads are arranged fan-wise and the pivot may be attached to a cell of Sertoli (spermatoblasts), but such appearances are uncommon. The central amorphous material generally shows a few intensely basophil, small, round, free nuclei. Staining of the spermatozoal heads is occasionally indifferent but no definite oxyphilia occurs. The stroma is minimal where the tubules touch and scanty in the interspaces. It appears to consist of a vascular tissue with large lymphatics, the only nuclei seen are those of connective tissue and endothelial cells.

The epididymis shows round or oval or irregular tubules lined by a regular columnar epithelium with long cilia. The cytoplasmic layer carrying the cilia is denser than elsewhere, and immediately beneath the free border it is loose and almost vacuolated. The nuclei are oval, moderately stained, closely packed, and rather indistinct in outline. There is no disintegration nor desquamation, but the epithelium has a somewhat cloudy appearance. Large numbers of well stained spermatozoa are present in most of the tubules.

The ovary presents numerous large corpora lutea in varying stages of development. Graafian follicles are not conspicuous and the lining cells are easily broken down. It is doubtful whether primordial ovules are recognizable. Occasional follicles are distended with fluid. The stroma contains great numbers of cells of which the cytoplasm is scanty, conglomerate and fibrillated, and the nuclei are round or oval and faintly and diffusely stained.

The Fallopian tube shows a well-marked muscular layer lined by a plicated columnar epithelium of which the cytoplasm is hyaline and the nuclei are large and stain moderately deeply.

Lungs.

The appearances recall those of slight localized emphysema owing to variation in size of alveoli. The alveolar walls are little vascular and the endothelial nuclei are small, irregular, contracted, and stain deeply and diffusely. The alveolar spaces are empty but may contain a few desquamated endothelial cells or red blood corpuscles.

The bronchi are lined by a plicated low columnar epithelium on which short cilia are occasionally seen. The cells are not sharply defined. The cytoplasm is continuous and hyaline, sometimes covered by a little amorphous material, but devoid of goblet cells and mucus. The nuclei are small, oval, deeply and diffusely stained and ill-defined owing to close packing. There is a well defined layer of peribronchial tissue in which are many endothelial cells and lymphocytes with the usual characters.

Thyroid Body.

The thyroid body is well marked and consists of acini varying much in size but filled with colloid in all but the smallest. The colloid is not vacuolated but sometimes is granular rather than homogeneous. The alveoli are lined by a low cubical epithelium with a small quantity of hyaline cytoplasm. The nuclei are round or oval, vary in depth of staining, but when faintly stained show a little dust-like or particulate chromatin. The stroma is scanty and not markedly vascular.

Salivary Gland.

The structure is well preserved. Serous and mucous types of gland are represented. In the serous type acini with basophil, finely granular cytoplasm are intermingled with acini having oxyphil but less granular cytoplasm. The nuclei of both varieties

of acini are round and moderately stained, but in the oxyphil variety they are a little larger and less deeply stained. In the mucous type the acini show a hyaline, voluminous, unstained cytoplasm with well defined cell outlines, possibly a few fine granules, and a contracted, moderately stained nucleus that is pushed against the basement membrane. The ducts in both types of gland agree in presenting a well marked oxyphil continuous hyaline cytoplasm and round or oval, faintly or moderately stained nuclei without particulate chromatin. The lumina are small but empty.

Lymphatic Gland.

Great numbers of lymphocytes are present, particularly towards the periphery or arranged in ill-defined foci. These cells appear to consist of naked, intensely basophil, small, round nuclei alone. Towards the centre of the gland a few large, round or oval or irregular, faintly and diffusely stained endothelial nuclei are visible. No plasma cells are present. Blood-vessels are few and there is no evidence of congestion. On prolonged search bare traces of nuclear débris are found.

Paraortic Tissue.

This tissue is lobulated and forms a narrow strip lying on either side of the descending aorta, both in thorax and abdomen. It appears to be directly continuous with similar material or fatty areolar tissue around the adrenals. It consists of large, irregularly polygonal cells with well defined outlines and filled with a finely foam-like or granular network. As a rule the nuclei are small, round or oval, deeply and diffusely stained, and more or less centrally placed. Between the cells minute empty canaliculi are visible and many small blood-vessels and capillaries permeate the tissue. Some of the cells show large fat lacunae at times and then a resemblance to fatty areolar tissue may result. Otherwise the tissue strongly recalls the cortical region of adrenal. Frozen sections stained with Sudan show enormous numbers of deep red globules of small to moderate size. Stained with osmic acid some of the larger globules stain intense black, but the major portion of the tissue is brown or grey. Moderate numbers of the globules are doubly refracting.

The Rat Exposed to Radium

The animals in this series fall into three main groups according as greater consideration is given to (*a*) increase in duration of exposure, (*b*) increased survival after exposure, or (*c*) increased exposure with survival. The three groups overlap to some extent.

A. *The Effect of Increase in Duration of Exposure.*

In this section all animals were killed immediately after exposure except the last which was found dead. They are as follows:

Number.	Length of exposure.	Number.	Length of Exposure.
Q 8	3 hours	Q 4	12 hours
Q 9	3 „	Q 11	16 „
Q 13	3 „	Q 23	16 „
Q 17	3 „	Q 6	24 „
Q 19	3 „	Q 2	46 „
Q 7	6 „	Q 1	48 „

The macroscopic appearances in animals of 3 hours' exposure do not call for remark. Occasionally the lungs are mottled or may contain foci of muco-gelatinous material, but probably this is independent of the exposure to gamma rays. The stomach is contracted and there are no signs of intestinal changes though, in one instance, the animal suffered from a diarrhoea when killed, which had not been noted before exposure. With 6 hours' exposure, contraction of stomach is replaced by distension and, with 24 hours' exposure or longer, the distension of stomach is great and some parts of the intestine are also distended and may contain blackened contents from admixture of blood. The intestinal contents, even in the rectum in such cases, are fluid, and there is much gas. The lungs, where the exposure has been 6 hours or longer, generally show patchy consolidation, and the bronchi may contain much mucus.

The microscopical appearances are as follows :

Blood.

Within the blood-vessels of animals exposed for 3 hours, the red corpuscles may be discrete or may cohere into a homogeneous mass, but, usually, staining is good or fair, and shape is good and even. Leucocytes are reduced in numbers and usually polynuclear cells predominate, but some lymphocytes are always seen. Nuclear staining in the leucocytes is rather poor.

In animals exposed for 6 hours or longer there is little alteration in respect of the red corpuscles, but some corpuscular débris may be found in cases of very long exposure. On the other hand the leucocytes show a progressive diminution in numbers so that a prolonged search is necessary to reveal even a few. Such leucocytes as are present are exclusively polynuclear in animals exposed for 16 hours or longer. Nuclear staining of leucocytes is poor.

Striated Muscle.

As a rule examination has been made of abdominal, bicipital of arm and thoracic muscle ; occasionally muscles of thigh have been examined in addition. In all situations, striation is poor in the paraffin sections, but good in those cut, frozen, and mounted in Farrant's medium. Under the last mentioned conditions it is rare for a fibre to be found devoid of striation, but this is not the case with muscle embedded in paraffin. A certain translucent or vitreous change is frequently present in embedded muscle and is associated with a patchy deposition of stain over the section as if an albuminous material lay between the individual fibres. This deposit is not seen in frozen sections. The intermuscular spaces

are not unduly large and, other than this albuminous material, no abnormal elements are present. The nuclei vary much in appearance according to the angle at which they are viewed. When seen on the flat they are rods with blunt ends, faintly and diffusely stained or may show a little dust-like chromatin. The mean of 50 measurements in each of the rats of this series indicates that, in abdominal muscle, the nuclear length is about 6 times the breadth.

In frozen sections stained with Sudan or scarlet, the muscle fibres show no avidity for the stain as a rule, but, occasionally, a fibre is seen which is distinctly pinker than its fellows, and in such a fibre there may be deposition of deeply stained, dust-like lipoid granules. These granules may be irregularly disposed or may be arranged along the lines of the normal striation of the fibre. The lipoid is singly refracting.

In animals after 6 hours' exposure striation may be moderately good, even in paraffin sections, but, as the length of exposure increases, it becomes very poor and only in places recognizable. Translucency of the fibres is marked and widespread, though the distribution is often patchy. A stained albuminous deposit is usual over the fibres and the distribution is irregular. The intermuscular spaces are wide but no adventitious cells are present. The nuclei vary greatly in appearance; often being contracted and staining deeply. The mean value of nuclear length in abdominal muscle for rats exposed 6–48 hours is 5·25 the breadth, for bicipital muscle it is 4·2. Nuclei suitable for measurements are relatively few; they show blunt, rounded ends and a small amount of dust-like chromatin on an almost colourless basis : the nuclear membrane is generally well defined. In frozen sections, striation is better than in material embedded in paraffin, but is less well marked than in animals with 3 hours' exposure. Diffuse pink staining of some of the fibres under Sudan or scarlet is fairly common, and dust-like lipoid may be seen, but these appearances are not invariable.

Unstriated Muscle.

Even amongst rats that have been exposed for a uniform period of 3 hours, variations are seen in the musculature of the gastro-intestinal tract. The muscularis mucosae seems to be most affected, but all coats show oedema in greater or less degree, and vacuolation may be present to such an extent that the inner coat of the stomach viewed in cross section is sieve-like. The degree of alteration of the muscle diminishes as one passes downwards, so that, in many cases, muscle of descending colon and rectum cannot be distinguished from the normal. Frequently the contractile material has a diffuse hyaline appearance recalling the translucency noted in striated muscle. Isolation of the fibres is unusual. The nuclei are elongated, often sinuous, deficient in chromatin, unless viewed on the edge, and usually stain diffusely, occasionally they are vacuolated. No lipoid has been found in unstriated muscle of intestine. In arteries and arterioles the appearances are similar, but clefts are common in the unstriped

muscle of arteries and the nuclei are contracted, irregular in shape and deeply stained. In arterioles the contractile material is diffusely hyaline, the nuclei are relatively large and numerous, irregular in shape, and stain faintly and diffusely. In Fallopian tube the tissue stains remarkably well, the nuclei are sharply defined, stain moderately deeply and are large and numerous, the contractile material is homogeneous and faintly stained.

Animals exposed for 6 hours or longer show, in the contractile material, an increasing oedema or vacuolation which extends widely over the stomach and intestines. Often little contractile material is recognizable in bundles that are cut transversely and such as remains is homogeneous and hyaline in composition. The intermuscular spaces are widely dilated. The nuclei vary greatly in shape but often are tortuous, much contracted, and stain deeply. They may lie definitely within lacunae or be attached to the sides of clefts or spaces. With the longer exposures the nuclei themselves become irregularly vacuolated, and it is common to find nuclei of which one portion is contracted and deeply stained while the rest is irregularly vacuolated. Sometimes the vacuolation has proceeded to such an extent that the nucleus is ruptured longitudinally. In arteries the appearances are similar to those described as obtaining in rats exposed for 3 hours, but the clefts are more numerous, the nuclei are more irregular in shape and staining and vacuolation is commoner. Throughout the whole subsection, particulate chromatin in the nuclei is unusual. The muscle shows no adventitious cells.

Cardiac Muscle.

In rats exposed for 3 hours, cardiac muscle usually stains well and shows nuclei of good shape and staining, striation is poor or moderate even for cardiac muscle and the fibres are finely granular. Occasionally vacuolation of the contractile material is seen, and isolated fibres may be homogeneous and translucent, but neither of these changes is common. The nuclei vary much in shape and staining. When viewed on the flat they are rods with nearly square ends and, on an average 5·3 times as long as broad, contain a very little finely particulate, deeply stained chromatin, and, very rarely, are vacuolated. Occasionally the space between the fibrils is widened, but no adventitious cells nor materials are present.

In rats exposed for 6 hours or longer, striation is poor as a rule, but sometimes a fibre will show good striation. A fine granularity of the fibres is marked, the granules being more densely packed than in the 3 hours' series. Fragmentation of the contractile material occurs and the intermuscular spaces are wide, but contain no adventitious cells nor definite evidence of oedema fluid. The nuclei may appear normal or may vary widely in appearance, even in the same specimen. Usually they present a few points of particulate chromatin on a clear and colourless base and they may be vesicular. On an average, nuclear length is 5·2 times the breadth. In no instance has a frozen specimen stained with Sudan or scarlet revealed the presence of lipoid.

Connective Tissue.

Few changes are noted in connective tissue beyond a tendency to granularity of the fibrils most marked in the loose varieties and with more prolonged exposures. Occasionally dense connective tissue appears collagenous. There is no great evidence of oedema and few adventitious cells are present. The fibrous tissue nuclei are contracted and stain deeply; there is no evidence of proliferation.

Endothelium.

In rats exposed for 3 hours the endothelium covering stomach and intestines is rarely in good condition. Very occasionally it is still adherent, usually it is detached in places and not infrequently large tracts have disappeared altogether. The layer is better over stomach and over large intestine than over the small intestine, and in small intestine the endothelial condition is worst over duodenum and jejunum. Here traces alone may be visible in which the nuclei are irregular in shape and staining is intense and diffuse when the nuclei are viewed in profile, faint and diffuse when they are seen in face. The cytoplasm is almost colourless and perhaps faintly granular, and the outline of the cells is very irregular. Within the blood-vessels the endothelium is generally well preserved, but there may be a little desquamation within the larger vessels and the nuclei may stain poorly. As a rule the endothelium of arterioles is excellent, the nuclei are deeply stained, small and project into the lumen owing to contraction of the muscular coat. In lung there may be a little desquamation and the cells. in that case, usually carry fine granules of black pigment. Within the substance of spleen and lymphatic glands the nuclei are faintly stained, irregular in shape but relatively large, and the cytoplasm is conglomerate. In both regions some of the endothelial cells may be much larger than their fellows and crammed with pale brown pigment or débris of red blood corpuscles.

In animals exposed for 6 hours or longer the endothelium over stomach may persist and stain faintly, but generally it is partially detached or has disappeared entirely. The nuclei may be vesicular and stain faintly, or contracted and stain intensely. Over the intestine the endothelium is affected in a similar way but to a greater extent. As a rule the degree of injury is greatest over duodenum and ileum and diminishes as one passes downwards. Within the large blood-vessels the endothelium is often detached or it may be irregular or wanting. The nuclei are distorted and staining is poor. In the small blood-vessels the nuclei are rounded, deeply stained and project into the lumen, there is no evidence of proliferation, and the appearances do not differ sensibly from the normal. In lung there may be a little desquamation, and the cells may contain blood pigment, but these appearances are not pronounced. Within the substance of spleen and lymphatic glands the endothelial nuclei are relatively large, irregular in shape, faintly stained, and sometimes vesicular; the cytoplasm is conglomerate. Pigment

may or may not be present in the cells and the general staining is poor and diffuse.

Liver.

In the animals exposed for 3 hours, the liver is generally somewhat congested, the capillaries and larger blood-vessels are widely dilated. The red blood corpuscles are frequently partially degenerated, and sometimes the blood channels contain only pale yellow granular material. Cohesion of the tissue is poor and the microscopic sections require careful handling—even those embedded in paraffin. The cytoplasm of the hepatic cells is granular and the cell outlines are poorly defined. The number of granules varies, and small groups of cells are affected similarly so that a patchy appearance often results. The nuclei vary in size and appearance. Usually they are round and present a small amount of particulate chromatin, a nucleolus and a well-marked nuclear membrane, but. in some cases, they vary within somewhat wide limits in size and 'ghosts' are found in considerable numbers. These 'ghosts' vary from a condition in which the nucleus is simply less well defined than usual, to one in which the nuclear membrane has disappeared and the chromatin is reduced to a small constellation of intensely stained points. Sometimes it would seem that a nucleus has disappeared altogether. The hepatic substance may present a few small focal necroses. The stroma shows small numbers of young connective tissue cells, but leucocytes are wanting as a rule. Disposed through the liver and frequently on the side of capillaries are isolated small, deeply stained nuclei which may be endothelial. The bile ducts lie in a fairly voluminous and cellular connective tissue and are lined by a single layer of cells with conglomerate cytoplasm and highly vesicular very faintly stained nuclei. The lumen is small but usually empty. In frozen sections stained with Sudan or scarlet there is little evidence of lipoid.

In rats exposed for 6 hours or longer, there is greater congestion, and portions of the tissue may have a parboiled appearance or actual foci of hyaline material (possibly altered albumin derived from the blood-vessels) may be found. The cytoplasm of the hepatic cells is granular and differs little from that found in 3 hours' specimens, but the nuclei are more frequently ghost-like or they may be empty sacs. At the first glance, sections of liver even from a rat exposed for 48 hours may appear little changed. The stroma and the bile ducts are similar to those in the 3 hours' specimens. Frozen sections afford even less evidence of lipoid.

Spleen.

In rats exposed for 3 hours the mean amount of spleen was 0.052 c.c. per cm. of length. The spleen tissue is somewhat devoid of nucleated cells, but red blood corpuscles are present in great numbers. The Malpighian corpuscles are usually evident and consist chiefly of endothelial and small monuclear cells. Lymphocytes may be present but are rarely found in considerable

numbers. A small amount of nuclear débris is often present in the Malpighian corpuscles and a few endothelial cells bearing pigment may be seen. The endothelial cells show a conglomerate cytoplasm and irregular, faintly stained nuclei. Little definite stroma is present in the organ. Over the spleen the endothelial layer is well preserved, but otherwise presents no special features.

In rats exposed for 6 hours or longer the mean amount of spleen was 0·024 c.c. per cm. of length. The spleen pulp is relatively acellular though the degree varies from case to case. Red blood corpuscles predominate greatly and may be well formed or partially broken down. Very few lymphocytes are found and, with exposures of 16 hours or more, they are almost absent. On the other hand endothelial cells, small mononuclear cells, and some plasma cells become conspicuous, though there is no evidence that their numbers are increased. The nuclei of these cells are irregular in shape and stain faintly. Nuclear débris is found chiefly in foci corresponding to the Malpighian corpuscles, but is not present in large quantity. Usually some large endothelial cells are found to be crammed with débris of red blood corpuscles.

Pancreas.

In animals exposed for 3 hours, as a rule the tissue is well preserved but has a cooked appearance. The acini show a hyaline cytoplasm which takes the acid stain frequently but may be basophil or indifferent. Usually the centre of the acinus is oxyphil, and the periphery, in which are the nuclei, is basophil. The nuclei are poorly defined and may stain deeply and diffusely or be vesicular and stain rather faintly. The outlines of individual cells are not distinguishable and a central canaliculus in the acinus is rarely recognized. The islands of Langerhans are small but distinct. The cytoplasm of the cells is conglomerate but irregular spaces may be visible in the island, the nuclei are small, round, and deeply and diffusely stained. The ducts lie in a relatively large amount of connective tissue that may be collagenous in appearance and are lined by a single layer of small, intensely vesicular, faintly staining nuclei.

In rats exposed for 6 or more hours, the pancreas is very well preserved but occasionally presents a cooked appearance in places. The cytoplasm of the cells is hyaline and definitely oxyphil especially after prolonged exposures, the outlines of contiguous cells are not discernible and there is no central lumen in the acinus. The nuclei are poorly and diffusely stained or may be vacuolated. Islands of Langerhans differ much in numbers, the cytoplasm is conglomerate and granular, the nuclei are even in size and stain deeply. The ducts are well defined and are lined by a single layer of highly vesicular, faintly stained nuclei.

Kidney.

In animals exposed for 3 hours there is often a little congestion of the small blood-vessels, including those of the glomerular tuft, but hæmorrhages are not seen. The tuft itself shows widely dilated vessels which may be empty or may show red blood

corpuscles. The endothelium lining Bowman's capsule and cover-
ing the tuft is well preserved, the nuclei of the cells are small,
somewhat contracted and irregular in shape, and, in most instances,
deeply and diffusely stained. Though isolated glomerular spaces
show a few red blood corpuscles or traces of albuminous material
in the majority of cases when search is made, the space is usually
empty. The convoluted tubules show a wide, irregular lumen
bridged by strands of coagulated albumin derived from partial
disintegration of the renal cells. The renal cells are often broken
down on the side towards the lumen of the tubule so that the
nuclei are exposed. The rest of the cytoplasm is hyaline or
slightly granular and very occasionally shows radial striation.
The outlines between contiguous cells are not visible. The nuclei
stain faintly, show a small amount of particulate chromatin and
frequently a nucleolus, but are well defined and even in size.
'Ghosts' are seen very occasionally. In the conducting tubules
the lumen is sometimes bridged by strands of coagulum but
usually is empty. The cytoplasm of the renal cells is very scanty
and the nuclei are often vesicular. Nevertheless the epithelium
of conducting tubules appears to have suffered less change than
that of convoluted tubules. The epithelium lining the pelvis of
the kidney consists of a single layer where it covers the papilla
and of several layers where it is passing into the ureter. The
nuclei are vesicular and shrunken from the cytoplasm. No
mitoses are seen. The stroma of the organ does not call for
remark.

In rats exposed for 6 hours or longer, congestion is marked but
there are no hæmorrhages The glomerular tufts may be swollen
and nearly fill Bowman's capsule, with the result that the
glomerular space is small, or the tuft may be shrunken. In
either case the glomerular endothelium is well preserved though
the nuclei are shrunken and stain deeply. The glomerular space
is usually empty. In the convoluted tubules the epithelium may
be greatly swollen so that the lumina are reduced to mere clefts,
or the inner portion of the cells may have broken down exten-
sively leading to a widely dilated lumen which is bridged by
strands of coagulated albumin. The cytoplasm of the renal cells
is cloudy and hyaline or finely granular. Disintegration of the
cells may be considerable. The nuclei vary somewhat in size, are
faintly stained, frequently show very little particulate chromatin,
though a nucleolus may be visible and 'ghost' forms are not
uncommon. In the conducting tubules the lumina are wide and
may show strands of coagulated albumin, but usually are empty.
Cytoplasm is scanty and vacuolation of the cells is common. In
some instances the cytoplasm has disappeared to such an extent
that the tubules appear to be lined by nearly naked nuclei.
Stroma and pelvic epithelium call for no special remark.

Adrenal.

In rats exposed for 3 hours the cortex is sometimes rather
vascular, shows numerous vacuoles indicating the former presence
of fat or lipoid globules, scanty, finely granular cytoplasm and

small, round, well defined, rather faintly and diffusely staining nuclei. The outlines of the cells are sometimes well marked and the cortex, internal to a regular zona glomerulosa, may be divided into an outer half where the vacuolation is greater and the cells are larger, and an inner half where the cells are smaller and vacuolation may be quite limited. Frozen sections stained with Sudan or scarlet show that the outer part of the cortex contains a large amount of large globules of lipoid while the inner part contains little, and that in the form of small globules. The medulla consists of a scanty, finely granular, conglomerate material in which are embedded numbers of relatively large, round, highly vesicular and faintly stained nuclei showing little particulate chromatin. Sometimes definite sinuses are seen in the medulla.

In animals exposed for 6 or more hours, the chief difference from the description given above lies in a greater vacuolation of the outer part of the cortex so that a section of adrenal appears greatly disintegrated. Outlines of cells are lost and the nuclei lie nearly naked in a scanty granular material. Similarly, disintegration of the medullary portion and ill-staining of the nuclei appear to be greater than in the 3 hours' specimens.

Stomach and Intestines.

In the 3 hours' specimens, the squamous portion of the *stomach* is thin. The Malpighian layer of cells is irregular, the nuclei are vesicular and faintly stained, and the cytoplasm has shrunk so that the nucleus frequently lies in a vacuole. Few layers of cells lie superficial to the Malpighian layer and the arrangement is very irregular, while the nuclei in these cells are so faintly stained as to be recognizable with difficulty. Eleidin granules are usually present in small numbers but stain deeply. There is a fair amount of desquamation of superficial keratinized layers. In the secreting portion of the stomach the epithelium of the tubular glands is usually contracted from the stroma and actual desquamation may have occurred. The cells are of two kinds —small, basophil, granular and ill-defined towards the blind ends of the tubules, and large, oxyphil, hyaline and well-defined towards the orifice. Basophil cells are not found at the orifice, but occasional oxyphil cells may be present at the blind end of the tubule. The nuclei of the two kinds of cell differ. In the basophil cell the nucleus is ill-defined and staining is deep and diffuse ; in the oxyphil cell the nucleus is often vesicular and though faintly stained is quite conspicuous. Superficial desquamation of epithelium has taken place, but there is no evidence of mucus formation. No mitoses are found. The stroma is very scanty, free from cells, and calls for no special remark.

In *duodenum* the mucous membrane is much disorganized, portions have desquamated and the entire stroma may be denuded. The cells show a granular and degenerated cytoplasm, nuclei are ill-defined but may be highly vesicular, and nuclear débris is often present at the blind end of the tubules. Usually goblet cells are numerous and mucus formation is pronounced, but occasionally

these features are wanting.   Mitotic figures are very rarely seen and, if present, are represented by ill-formed masses of intensely stained chromatin.   The stroma is fairly voluminous and contains many endothelial and small mononuclear cells; polynuclear leucocytes are completely wanting and plasma cells are few.   The lumen of the gut usually contains a limited amount of desquamated and degenerated material mixed with mucus.   In *jejunum* the appearances resemble those found in duodenum but are perhaps a little less intense.   Desquamation may be widespread and the denuded stroma may be partially necrotic.   No mitoses are found.   In *ileum* the mucous membrane is less voluminous and the appearances may vary somewhat from place to place.   In general they resemble those found in duodenum but goblet cells are more numerous, mucus formation is more intense, destruction of epithelium is less severe.   Nevertheless sloughing of the entire mucous membrane is met with occasionally.   The stroma is relatively more voluminous and contains many cells chiefly endothelial and small mononuclear.   Plasma cells may be fairly numerous.   No mitoses are found.

In *colon* the chief characteristic is an intense formation of mucus.   The investing columnar epithelium is usually well preserved, but great numbers of the columnar cells lining the tubular glands are converted into goblet cells which may be full or may have discharged their contents.   In the remaining columnar cells the nuclei are vesicular and faintly stained.   The stroma is scanty and often oedematous.   The cells present are chiefly endothelial, plasma or small mononuclear, but their numbers are not great. No mitoses are found.   In *rectum* the mucous membrane is less voluminous and the mucus formation is generally less intense. The investing epithelium is well preserved and, in the tubular glands, the appearances resemble those found in colon but are less pronounced.   The stroma is scantily cellular, but a few plasma cells may be present.   No mitoses are found.

In rats exposed for 6 hours or longer the squamous portion of the *stomach* shows a very irregular, ill-defined Malpighian layer in which the nuclei are little more than empty sacs, staining very feebly.   The granular layer contains few but well-marked eleidin granules and there is considerable desquamation of structureless superficial keratinized layers.   The secreting portion varies somewhat according to the length of exposure.   Usually the two varieties of cells, basophil and oxyphil, that line the tubular glands are recognizable, but the nuclei become ' ghosts ' or sac-like and stain very faintly with longer exposures and there may be actual desquamation.   Some mucus may be found, but it is not a prominent feature, and goblet cells are not found.   Mucus is absent in exposures of 24 hours or longer.   The stroma contains few cells, but the lymphatic channels in the submucosa are widely dilated.

In *duodenum* a similar difference is noted according to length of exposure.   Below 16 hours the mucous membrane is swollen and covered by a fair investing layer of columnar epithelium in which many goblet cells are present but there is some desquamation.

Within the tubules the epithelium has broken down and much has separated from the basement membrane. Nuclear débris is found in the blind ends of the tubules, such nuclei as persist are vesicular and stain poorly and goblet cells and mucus formation are marked. Under an exposure lasting 24 hours or longer, disintegration and desquamation of the mucous membrane is advanced and traces alone may persist. Entire casts of tubular glands are formed by the desquamated epithelium and such cells as remain show a granular disintegrating cytoplasm and sac-like, faintly stained nuclei. Changes occurring in the stroma do not vary so greatly with length of exposure. In the whole group it is oedematous and may show fair numbers of mononuclear and plasma cells. Where the mucous membrane has desquamated, the superficial layers of the denuded stroma may show paucity of cells and early necrosis. With shorter exposures the lumen of the gut contains a small amount of desquamated epithelium, but, with longer exposures, it contains entire tracts of degenerated mucous membrane mixed with mucus.

In *jejunum* the changes resemble those found in duodenum but are more intense ; partial sloughing of denuded stroma is usual. The quantity of mucus present varies within wide limits, but is generally great. Such columnar cells as persist are highly granular and the nuclei may be sac-like or actually undergoing disintegration.

In *ileum* the condition resembles that found in duodenum, but occasionally is not quite so advanced. Desquamation occurs, and the entire mucous membrane may be separated as a cast. Goblet cells are numerous and much mucus is present. Nuclear débris may occur in the tubular glands, but is not common. The stroma is oedematous and desquamation of epithelium may have laid it bare in places. Staining of the cells present in the stroma is often poor.

In *colon* the great feature is the extensive goblet cell and mucus formation. The general arrangement of the mucous membrane is preserved except under the most prolonged exposures when desquamation occurs. Otherwise the columnar cells are almost universally converted into goblet cells. The stroma is scanty and contains few cells, the submucosa is highly oedematous. The lumen of the intestine invariably contains much mucus. In *rectum* the appearances resemble those found in colon, but may be slightly less marked. Throughout the entire intestine, there is no evidence of mitoses.

Generative System.

Testicle. (4 animals.) In animals exposed for 3 hours, the tubules are a little shrunken, but usually show fair numbers of cells and masses of spermatozoal tails in the centre of the tubule. The cells of Sertoli are faintly stained and show large, oval, very faintly stained nuclei. Spermatogonia are approximately normal in appearance and form a regular layer of small cells with deeply and diffusely staining, small, round nuclei and little cytoplasm. Internal to these are irregularly disposed layers of spermatocytes,

of which the nuclei are pale and often sac-like, the most con-
spicuously degenerated nuclei lying close to the centre of the
tubule. Spermatoblasts and spermatids are uncommon, and when
found, the nuclei are usually, but not invariably, basophil. In
the case of fully formed spermatozoa the head is generally in-
tensely basophil, but this is not invariably the case. The tails are
oxyphil and show some tendency towards granular degeneration.
The inter-tubal material is scanty and shows a few small blood
vessels and endothelial cells. In the epididymis the lining cells
are well preserved and form a regular columnar lining for the
tubules, but cilia are not always seen. Spermatozoa may be
present in numbers or the tubules may be empty; when present
the spermatozoa generally stain fairly well. No mitoses are
seen.

In animals (6) exposed for 6 hours or longer the cellular
elements within the tubules show much change, especially under
the longer exposures. In many cases the cells seem to have
disappeared almost entirely so that the tubules contain only a
little débris and some broken-down cell forms. Sometimes, on
the contrary, the cells are fairly preserved, but present changes
in their staining reactions. Where they are not broken down
the spermatogonia present the usual intensely basophil, diffusely
staining nucleus and an occasional mitotic form is visible; but
the nuclei of spermatocytes are frequently indifferent in reaction
or even definitely oxyphil. Spermatoblasts occur but are poorly
formed, and spermatids and heads of spermatozoa are usually
basophil, though indifferent and even oxyphil forms are not
uncommon. The inter-tubular substance is scanty and calls for
no special remark. In the epididymis the lining cells are well
preserved, and cilia are often seen, especially when the exposure
has been prolonged. On the other hand, spermatozoa are dis-
integrated into a granular material and the heads no longer take
the basic stain intensely, but may stain poorly or even take the
acid dye.

Ovary. Only 2 specimens were obtained, 1 from an animal
exposed for 3 hours, the other from an animal exposed for 46 hours.
In the 3 hours' specimen large corpora lutea were present in
various stages, but very little ovarian stroma was present and no
normal Graafian follicles. In the 46 hours' specimen the ovarian
stroma was much broken up and normal Graafian follicles were
absent. On the other hand, numerous round or oval cavities
containing degenerated ovular material were scattered through
the organ. One corpus luteum was present. In both instances
the Fallopian tube showed a plicated or polypose arrangement of
its lining membrane and some local desquamation.

Lungs. Bronchi. Trachea.

In the 3 hours' specimens the pulmonary tissue shows a little
congestion or even consolidation, and the alveoli may contain
a few red blood corpuscles, or polynuclear cells and desquamated
endothelial cells, or some granular débris, the result of oedema.
The bronchi usually show a well-preserved lining columnar

epithelium without much mucus or proliferation of cells. They are surrounded by a lymphoid tissue in which disintegration of lymphocytes leads to the presence of a relatively large amount of nuclear débris. The tracheal mucous membrane may be irregular and yield evidence of cell proliferation, or even may be partially detached. Often mucus is present in fair quantity and goblet cells are numerous, while there is a moderate degree of oedema of the sub-mucous tissue and the mucous glands contained therein.

In animals exposed for 6 hours or longer the pulmonary tissue may be fairly normal, but usually presents consolidated areas intervening with emphysema, and occasionally the consolidation is so considerable that it recalls lobar pneumonia. Mucous and caseous cavities may also be present, but probably are independent of the exposure to radium. The bronchi show no noteworthy changes of the lining epithelium and, in particular, no excessive formation of mucus, but the peribronchial tissue consists almost entirely of endothelial cells and plasma cells with some nuclear débris. Lymphocytes are practically absent. The tracheal mucous membrane resembles that found in the 3 hours' specimens.

Thyroid Gland.

In rats exposed for 3 hours the layer of cuboidal cells lining the vesicles is well marked, but the cells may be vacuolated or flattened and, in one instance, early calcification was seen. The nuclei vary much in appearance, being irregular and diffusely stained, or contracted and intensely stained. The colloid also varies much in quantity, and in some alveoli there may be very little, but it is rarely completely absent.

Amongst animals exposed for 6 hours or longer there is reason to believe that the colloid shows increasing tendency to disappear. Amongst rats killed immediately after an exposure of 6 hours or more, and therefore falling into the present group, the thyroid was preserved in only one. It showed partial disappearance of colloid from some of the alveoli. No difference has been detected in the appearance of parathyroid.

Paraortic Tissue.

In animals exposed for 3 hours, the appearance of this tissue was that of a lobulated material built up of polyhedral cells in which the cytoplasm was foam-like or showed lacunae and the nuclei were small and round. The amount of fat or lipoid varied, but usually was considerable, though it might be present in large globules when the embedded specimen revealed large lacunae in the cells or as minute globules when it gave rise to a foam-like cytoplasm. The degree of vascularity varied. Frozen sections stained with Sudan or scarlet showed the tissue to be crammed with lipoid. Under osmic acid the neutral fat was confined to the larger globules. No certain differences from the above were observed in animals that had been exposed for 6 hours or longer.

Lymphatic Gland.

In rats exposed for 3 hours, the appearances may vary within the same animal, but it is common for lymphocytes to be present in large numbers, accompanied by endothelial cells, small mononuclear cells, and often some plasma cells. Little or much nuclear débris is constant. In animals exposed for 6 hours or longer there is evidence of progressive destruction of lymphocytes. Few, if any, are found in the sections, but endothelial cells, small mononuclear cells and plasma cells are present along with considerable amounts of nuclear débris. Many of the endothelial cells are crammed with pale yellow pigment derived from broken-down red blood corpuscles. In animals exposed for 48 hours no lymph glands were found with certainty even though express search was made.

Salivary Gland.

The mucous and serous types of salivary gland are present and the latter shows two varieties of acini, viz., somewhat smaller acini, with numerous fine basophil granules, and larger acini, with fewer fine oxyphil granules and more sharply defined nuclei. These acini are intermingled, and the degree to which oxyphilia exists varies, so that probably the one variety is derived from the other. The cells of the acini are not well defined, and a central canaliculus is rarely seen. The mucous type shows acini in which the cells have undergone mucoid degeneration and swelling, so that the cytoplasm is almost clear, and the nucleus—contracted and deeply stained—is thrust against the basement membrane. The partitions between adjacent cells of the acinus are well defined. The ducts are lined by a columnar epithelium with oxyphil cytoplasm and vesicular nuclei. The lumen is small and empty. It is not certain that increased length of exposure is accompanied by histological change in the salivary glands, though occasionally, under prolonged exposure, the nuclei are vesicular, or vary greatly in size, and the ducts show the presence of coagulated material.

B.   *The Effect of increased Survival after Exposure.*

The effect of survival can be studied by comparison of the appearances met with in those animals killed immediately after an exposure of 3 hours (Nos. 8, 9, 13, 17, and 19 above), and the following, which were killed at varying times after an exposure of 3 hours.

No.	Survival.
Q 14	3 days
Q 18	3 ,,
Q 20	4 ,,
Q 15	6 ,,
Q 21	6 ,,
Q 16	9 ,,
Q 22	9 ,,

Nos. 14, 18, 20 may be regarded as a single group so that periods of survival may be taken as 3, 6, and 9 days.

Blood.

At 3 days the red corpuscles are of good shape and stain well, but are degenerate in some regions. Leucocytes are very rarely seen, and may be exclusively polynuclear ; sometimes staining is so poor that the variety cannot be determined. At 6 days, lymphocytes and polynuclear cells are approximately equal in numbers, but the totals are still small. At 9 days, the totals of leucocytes are small and the predominant variety is uncertain. The blood-vessels contain some granular material or fibrin, but the red blood corpuscles are discrete and stain well.

Striated Muscle.

At 3 days, abdominal muscle shows very poor striation, a considerable amount of patchy translucency and irregular fibrillation. Nuclear staining is faint but well defined, and the nuclei show a small amount of dust-like chromatin. A little albuminous material is irregularly disposed over the muscle fibres. Bicipital muscle is similar, but the striation is better and translucency of the contractile material is less. Thoracic muscle varies, but striation is better than in either of the other situations and translucency is less. In frozen sections striation is uniformly more regular and better defined. Stained with Sudan or scarlet occasional fibres take the dye, and dust-like lipoid globules were noted in some fibres of one case.

At 6 days, striation is poor and there is less translucency of contractile material. The nuclei stain well and show dust-like chromatin but are somewhat swollen. The abdominal muscle shows the most pronounced changes and the thoracic muscle the least. Frozen sections reveal poor striation, some staining of individual fibres with Sudan, but no lipoid deposit was found.

At 9 days, the appearances vary and there may be evidence of oedema or of local proliferation of muscle nuclei. Striation is poor or wanting, translucency of contractile material is much less in biceps, absent from thoracic muscle but still present in abdominal muscle. The nuclei are swollen and oval in shape, stain faintly, and show dust-like chromatin, but are well defined. In frozen sections striation is poor, there is some staining of individual fibres and dust-like lipoid deposit may be present.

Unstriated Muscle.

At 3 days, gastric muscle shows little or much vacuolation of the contractile material and some vesicular or otherwise degenerate nuclei. In duodenum the muscle is slightly oedematous or vacuolated or the fibres are broken, the nuclei are irregular in shape and staining and contain little particulate chromatin. In jejunum the appearances are similar but intensified. In ileum there is oedema, the nuclei are distorted and stain badly and the contractile material is deficient in quantity. In colon the contractile material is oedematous or vacuolated or shows clefts and the nuclei are often vesicular or lie in lacunae and contain little particulate chromatin. In rectum the appearances resemble those of colon but are not so intense. In artery there is much

variation, but usually there is vacuolation of contractile material and the nuclei are plump and stain faintly, showing but little particulate chromatin.

At 6 days, stomach shows great vacuolation or fenestration of contractile material and the muscle nuclei are vesicular and distorted. In duodenum the contractile material is much swollen and the nuclei are barely recognizable. In jejunum the appearances are similar but there may be vacuolation. In ileum the conditions are less intense. In colon the muscular tissue has a boiled appearance and the nuclei are irregular in shape and stain faintly. In rectum there is oedema or vacuolation of contractile material but the nuclei stain fairly well and show dust-like chromatin. In artery clefts are present and the nuclei are pale, vesicular or contorted.

At 9 days, gastric muscle shows some clefts or lacunae in the contractile material and the muscle is thin; the nuclei are small and contracted or irregular in shape and may stain intensely or very faintly and diffusely. In duodenum the coats are thin and there is some vacuolation; the nuclei are regular and fusiform in shape and stain faintly and diffusely. In ileum the conditions are similar but the nuclei may be plump. In colon the contractile material is swollen and may be vacuolated, the nuclei stain faintly and may be highly vesicular. In rectum the conditions are similar. In larger arteries the contractile material is broken and the nuclei are variable in size and shape and often vesicular. In arterioles the contractile material may be fibrillated but is swollen and translucent; the nuclei are contracted and irregular in shape and stain faintly.

Cardiac Muscle.

At 3 days, there is poor striation, some fine granulation and occasional translucency of isolated fibres; the nuclei show traces of dust-like chromatin and, rarely, are vesicular. The intermuscular spaces are somewhat wide but show no adventitious material or cells.

At 6 days, a trace only of striation is found, the fibres are granular and may be friable, the nuclei vary in size and shape, stain faintly and show dust-like chromatin.

At 9 days, very little striation is found, fine granulation is marked, there is no translucency; the nuclei may be rather deeply stained rods, or may be swollen or vesicular and present the merest trace of chromatin. There are no signs of inflammation or of oedema. Frozen sections give no evidence of lipoid throughout the entire series, but striation is fairly good.

The ratios of nuclear length : breadth were for 3 days survival 5·5 : 1, for 6 days 5·6 : 1, for 9 days 5·3 : 1.

Connective Tissue.

At 3 days, there is some granularity of the fibrils of loose connective tissue and there may be swelling of nuclei in the dense variety.

At 6 days, the granularity is marked, and at 9 days the

fibrils of both loose and dense varieties may be collagenous or granular, and there may be evidence of former oedema.

Endothelium.

At 3 days, over stomach and intestines the endothelium is loosely attached or much detached and fragments alone are adherent in many regions. The nuclei usually stain deeply when viewed in profile; faintly and diffusely, when seen in face. Vesicular nuclei occur but are not common.

At 6 days, the endothelium over stomach and duodenum is detached and shreddy, but, over the rest of the intestine, may be moderately adherent or detached and fragmentary. The nuclei may be barely recognizable, but, when seen, are usually swollen, degenerate, and faintly stained.

At 9 days, over stomach the endothelium is fairly good; over the intestines, patches are adherent but the nuclei are often swollen and vesicular and differentiation between cytoplasm and nucleus may be difficult.

The endothelium lining arteries varies within somewhat wide limits but usually is fair, though vesicular nuclei and faint staining may occur. In small blood-vessels the endothelium is generally good, the nuclei are seen in profile and stain deeply. Endothelium covering spleen, at 3 days, is well preserved. The nuclei are linear and stain intensely, but, at 6 days or 9 days, it may have broken down or disappeared in large part and such cells as remain are swollen. The nuclei still stain intensely. Within the substance of the organ the nuclei are irregular in shape, stain faintly, and may be vesicular, the cytoplasm is conglomerate or broken down. The changes are similar at 3, 6, and 9 days.

In lung there is some evidence of slight desquamation of alveolar endothelium in the 6 and 9 days' specimens.

Liver.

At 3 days, the tissue is moderately congested and coherent but the red blood corpuscles show disintegration. The hepatic cells are granular, the outlines indistinct, the nuclei are round, even in size, are faintly stained, show a little particulate chromatin and a nucleolus. 'Ghosts' are found in considerable numbers.

At 6 days, cohesion of hepatic tissue is less and there is no congestion, but the red blood corpuscles are breaking down and granular material is found within widely dilated capillaries. The hepatic cells are coarsely granular and a patchy appearance results from the unevenness with which the granules are distributed through the liver and the extent to which they have disappeared from some regions. The nuclei are large and round, faintly stained, nucleolated, and great numbers are ghost-like.

At 9 days, cohesion of liver is poor, much of the cytoplasm of the hepatic cells has disappeared and the remainder is coarsely granular. The number of granules varies from place to place

and, where few, the cell membrane is visible. The nuclei are round, may be diffusely stained, or show particulate chromatin and nucleolus ; frequently staining is so faint that such granules as remain obscure the nucleus. Ghost-like forms are not so numerous as at an earlier date, but the impression is given that nuclei are less numerous than usual. In frozen sections stained with Sudan, very little lipoid is found in 3 days' specimens and none at 6 or 9 days. The bile ducts do not call for remark.

Spleen.

At 3 days, the spleen constitutes, on an average, 0·032 c.c. per cm. of body length. It is acellular, lymphocytes are infrequent except in the Malpighian corpuscles, and the chief cells present are endothelial cells and red blood corpuscles. Generally a few plasma cells are found and some of the endothelial cells may be swollen with pale yellow corpuscular débris or pigment. There may be a little nuclear débris, particularly amongst the cells of the Malpighian corpuscles. The stroma is scanty.

At 6 days, the mean value of the spleen is 0·0285 c.c. per cm. of body length. The tissue is relatively acellular and endothelial cells or small mononuclear cells are nearly the sole nucleated cells found. Red blood corpuscles are present in great numbers. Malpighian corpuscles are moderately evident but contain few lymphocytes, and nuclear débris is not found. The stroma is scanty and delicate : in large part it appears to consist of the conglomerate cytoplasm of the endothelial cells.

At 9 days, the mean value of the spleen is 0·016 c.c. per cm. of body length. It is moderately cellular, endothelial and mononuclear cells are far more numerous than lymphocytes, and nucleated cells dominate the picture. The red blood corpuscles are often broken down. Malpighian corpuscles are not conspicuous and there is no nuclear débris. The stroma appears to form a larger and denser part of the spleen pulp.

Pancreas.

At 3 days, the general preservation of structure is moderate. the reaction of the cytoplasm varies but the centre of the acinus is usually faintly oxyphil. The nuclei are ill-defined and stain intensely and diffusely. Islands of Langerhans are well defined, the nuclei are round, stain deeply and diffusely and lie in conglomerate granular cytoplasm.

At 6 days and 9 days, preservation is better on the whole, but the differences from the 3 days' specimens hardly lend themselves to description.

Kidney.

At 3 days, vascularity varies and small haemorrhages may be noted. In the glomerular tuft the vessels are widely dilated. though the tuft itself is contracted. The endothelium lining Bowman's capsule and enveloping the tuft is well preserved, but the nuclei are irregular in shape and do not stain very deeply. The glomerular space is empty as a rule. In the convoluted

tubules some disintegration of epithelium is present, the lumen
is wide or partially obstructed and bridged by strands of
coagulum, but no definite casts are found. The nuclei of the
renal cells differ widely in size, usually stain fairly deeply,
present particulate or dust-like chromatin, and may be nucleo-
lated. In the conducting tubules the lumina are wide and may
contain hyaline casts, the cytoplasm is very scanty, the nuclei
are round, often vesicular, or may show dust-like chromatin and
a nucleolus.

At 6 days, there may be definite haemorrhages into the
kidney or vascularity alone may exist. The glomerular tufts
are shrunken but the capillaries are widely dilated. The endo-
thelium covering the tuft shows intensely stained, oval or even
vesicular nuclei, but that lining the capsule is poor and the
nuclei stain faintly. The glomerular space contains, in many
instances, coagulated albumin or red blood corpuscles. In the
convoluted tubules the lumen is wide and numerous bridges of
coagulated albumin and broken-down cytoplasm are present.
The renal cells are partially disintegrated and the nuclei are
large and pale, but vesicular forms are not found. In the con-
ducting tubules the lumina are wide, may contain traces of
albumin but usually are empty. The cytoplasm is very scanty
and the nuclei are often vesicular or show particulate chromatin,
and stain rather deeply.

At 9 days, there is no special vascularity and haemorrhage is
not found. The glomerular tufts are contracted and the capillaries
are widely dilated. The endothelium lining Bowman's capsule
and that covering the tuft is moderately preserved ; the nuclei
are irregular in shape but may stain intensely or rather faintly.
No red blood corpuscles are found in the glomerular space, but
there may be a little granular albuminous material. In the con-
voluted tubules the epithelium is broken down to a greater or
less extent and the wide lumen of the tubule is bridged by dis-
integrated and coagulated cytoplasm. The nuclei of the renal
cells stain rather darkly but may show particulate chromatin.
In the conducting tubules the epithelium may be profoundly
disorganized or merely detached, but, even in the latter instance,
vesicular or otherwise degenerated nuclei are often seen. By the
9th day earlier changes may have receded or have become
intensified so that there is wider variation in the appearances.
The other renal elements do not call for remark.

Adrenal.

At 3 days, the zona glomerulosa is narrow and presents no
special appearances. The outer two-thirds of the cortex shows
numerous large lacunae the former seat of fat globules, and the
remaining cytoplasm is scanty and granular ; the inner third
shows smaller and fewer lacunae and a more densely granular
cytoplasm. The nuclei are faintly stained, small, and round, and
the cell membranes are usually well marked. In the medullary
portion are definite sinuses and the cells show a conglomerate,
rather scanty, finely granular cytoplasm in which are relatively

large, round, vesicular nuclei with a very little dust-like chromatin.

At 6 days, the cortical cells lack definition and the nuclei come to lie in clear spaces owing to the number of lacunae and the small amount of unaltered cytoplasm left. Frequently the cortex has a 'mossy' appearance. Nevertheless the condition of the cells varies from place to place. The nuclei are round, nucleolated and stain moderately deeply. In the medulla an alveolar arrangement is visible, but the cytoplasm has broken down and the nuclei are often vesicular.

At 9 days, the appearances are not sensibly different from those at 6 days.

Stomach and Intestines.

At 3 days the squamous portion of the stomach shows a very poorly stained and irregular Malpighian layer, vesicular nuclei, few eleidin granules and much desquamation of the keratinized layers. At 6 days, a similar condition obtains. At 9 days, the tissue is thin and represented by little more than a single layer of vesicular nuclei, a few eleidin granules and numerous desquamated and structureless keratinized layers.

The secreting portion of stomach at 3 days shows basophilic and oxyphilic cells in the tubules of the mucous membrane, but those with basophil granulations may be nearly absent. Many of the nuclei are vesicular and some desquamation is present. At 6 days, the appearances are similar. At 9 days there is definite formation of mucus and many of the cells have undergone mucoid degeneration, basophil and oxyphil cells are present, and many of the nuclei are intensely vesicular, but others show dust-like chromatin.

Duodenum. At 3 days, a variable degree of desquamation of the investing epithelium has occurred. The lining epithelium of the tubules is distorted in shape, the cells and nuclei are ill-defined and stain faintly, and a few doubtful mitotic figures are found. The stroma is highly cellular, perhaps denuded and necrosing superficially. The chief cells present are endothelial, small mononuclear and plasma cells. The submucous connective tissue is oedematous. Mucus may occur in the lumen of the gut.

At 6 days, definition is so poor that it is often difficult to distinguish nuclei from cytoplasm, much desquamation has occurred, there may be a little formation of mucus, fair numbers of goblet cells are present and doubtful mitotic figures are found. The stroma is scanty but may be oedematous. Cells are not unduly numerous, and are chiefly small mononuclear and a few plasma cells.

At 9 days, the investing epithelium may persist, but, if so, the cells are poor in shape and staining, having undergone mucogranular degeneration. In the tubular glands the cytoplasm is often vacuolated, the nuclei vesicular, goblet cells are numerous and much mucus is present. Deformed mitotic figures occur in fair numbers. The stroma is scanty, loose, and contains some small mononuclear, endothelial and plasma cells.

Jejunum. At 3 days, the appearances are similar to those of

duodenum but may be more marked or less marked in individual cases.

At 6 days, the same obtains but goblet cells are numerous, mucus is present in considerable quantities, and the nuclei of the columnar cells lining the tubules are highly vesicular. Deformed mitotic figures are numerous. The stroma is loose and voluminous and may contain a few lymphocytes in addition to endothelial, small mononuclear and some plasma cells.

At 9 days, the appearances are similar but evidence of mucus formation is increased, and many of the goblet cells are empty.

Ileum. At 3 days, the appearances resemble those described for duodenum and jejunum but vary in degree in individual cases.

At 6 days, goblet cell formation or mucus formation is pronounced and the lumen of the gut contains free mucus and desquamated epithelium. Deformed mitotic figures are numerous. The stroma is loose and voluminous, is not excessively cellular, and the cells present are endothelial, small mononuclear, and a few plasma cells.

At 9 days, the appearances vary, sometimes the mucous membrane is better than at an earlier date ; at other times, it is definitely worse. Correspondingly the formation of mucus and the number of goblet cells vary in individual cases. Doubtful mitotic figures are numerous. The stroma calls for no special remark.

Colon. . At 3 days, there is a good investing epithelial layer and the nuclei may stain moderately or be vesicular. In the tubular glands, goblet cells are very numerous and such columnar cells as intervene show vesicular nuclei. Actual mucus may be present in large quantity or be wanting. Mitotic figures are present, some cases with certainty, in others they are doubtful. The stroma is scanty but shows plasma cells and a few mononuclear cells.

At 6 days, the appearances are similar.

At 9 days, goblet cells and mucus formation are even more pronounced, but the other features are similar. Mitoses are few, stroma is scanty and contains few cells.

Rectum. At 3 days, there is much mucoid degeneration of the cells lining the tubular glands and the nuclei are vesicular in most cases. Mitotic figures are few and doubtful, stroma is loose, possibly voluminous, but relatively few cells (mononuclear, endothelial, and plasma) are present.

At 6 days, the appearances are similar but goblet cell formation and production of mucus are intense. Mitotic figures are few and doubtful.

At 9 days, goblet cells are fewer and there is a diminished amount of mucus but the cells of the tubular glands appear to be in a condition of mucoid degeneration. Mitotic figures may be present or absent. The stroma is scanty and carries few cells.

Generative System.

Testicle. At 3 days, the seminal tubules contain few cells. Cells of Sertoli are fairly formed but the nuclei may be degenerated

and stain more faintly than usual. Spermatogonia are moderately well formed and the nuclei are intensely and diffusely stained. Spermatocytes are moderately formed and the nuclei stain faintly and diffusely. Spermatoblasts are present but may be well or ill formed. Spermatozoa show all stages of staining of their heads from intensely basophil to definitely oxyphil, and an indifferent or slightly basophil staining is the rule. The tails are oxyphil. The intertubular substance is scanty and consists of a vascular connective tissue enclosing some endothelial cells. The tubules of the epididymis are lined by a well-formed ciliated columnar epithelium and are mostly empty, but a few remnants of spermatozoa may be present.

At 6 days, there is general disorganization, no good spermatogonia are found, spermatocytes are irregular in shape and staining, occasionally a spermatoblast is seen. The spermatozoa are degenerated and staining of the head, though usually basic, is often indifferent or even oxyphil. The epididymis shows good ciliated epithelium and stains well.

At 9 days, disorganization is not so great but many of the cells lie loose in the tubules, definition is poor and staining is faint. Spermatozoal tails are swollen and heads stain indifferently. In the epididymis, the tubules may be empty or contain spermatozoa. The shape and staining of the ciliated columnar cells lining the tubules are good.

Ovary. At 3 days, the specimen was almost entirely composed of corpora lutea, some of which showed a central liquefaction cavity, while in others, cells were undergoing fatty degeneration. No normal Graafian follicles were found. The nuclei of the stroma were larger and vacuolated but contained some dust-like chromatin.

At 6 days, the specimen showed large corpora lutea, some of which were centrally liquefied, others partially fibrotic and, in either case, vacuolation of luteal cells was common. No normal Graafian follicles were present but there was a good germinal epithelium. The stroma was scanty and loose, the cytoplasm of the cells vacuolated, and some mucoid degeneration was present.

At 9 days, the ovary was composed almost entirely of corpora lutea containing large vacuolated cells or degenerated material. No normal Graafian follicles were found but follicles of various size were present in which cellular degeneration had taken place in different degrees: frequently there was a central cavity surrounded by a partially broken layer of highly disorganized cells. The stroma was congested, loose and delicate, and contained small, round nuclei. The appearances somewhat suggested the intermediate (endocrine) substance commonly found in ovary of rabbit.

The Fallopian tube showed some mucoid degeneration of the lining mucous membrane at 6 days and, at 9 days, this was conjoined with local proliferation of the columnar cells and vacuolation of the cytoplasm.

Lung and Air-Passages.

At 3 days, the pulmonary tissue shows a small amount of emphysema and some of the adjacent regions may be collapsed. There is little desquamation of endothelium but red blood corpuscles may be found in the alveolar spaces. In the bronchi there is more or less desquamation often with mucoid degeneration of the columnar cells or the production of goblet cells. There is peribronchial accumulation of cells, mainly such as are found in chronic inflammatory conditions. In the trachea there is degeneration and desquamation of the lining epithelium, the cells are vacuolated and the nuclei vesicular. A certain amount of granular albuminous material but not much mucus is found along with the desquamated epithelial cells. At 6 days the appearances are similar but there is less desquamation both in large and small air-passages. Nevertheless the mucous glands in the tracheal submucosa appear to be active. At 9 days, the appearances vary. There may be slight bronchopneumonia and peribronchitis, and some desquamation of endothelial cells occurs. In the trachea and bronchi the epithelium is present but the cytoplasm is irregular in shape or disorganized and vacuolated and the nuclei stain diffusely and moderately. The submucosa may be oedematous and the mucous glands are active. On the other hand extensive degenerative changes may be present.

Thyroid Body.

At 3 days, many of the vesicles show a diminished amount of colloid and traces alone may be present in some. The organ is often cellular between the acini but the cells are not inflammatory. There is a single layer of cuboidal cells lining the acini and the nuclei are contorted or contracted in shape, usually deeply and diffusely stained.

At 6 days the majority of acini are half empty and many of the smaller acini are completely empty while there may be partial disorganization of the tissue. The lining cells are cuboidal, often vacuolated, and the round or oval nuclei stain intensely and diffusely.

At 9 days, the colloid is shrunken or vacuolated or no colloid is found in some of the vesicles or the colloid material is replaced by an oedema-like fluid. The cytoplasm of the cells is scanty, partially desquamated and broken down or swollen and vacuolated, the nuclei are round or irregular in shape, moderately deeply stained and may lie in lacunae owing to vacuolation of the cytoplasm.

No changes have been detected in parathyroids.

Paraortic tissue.

At 3 days, the tissue presents lobules of large polyhedral cells in which the cytoplasm is coarsely foam-like, occasionally the foam is fine meshed and sometimes the cells appear to contain no cytoplasm. The nuclei vary in shape but usually are small, round or oval and stain moderately and diffusely ; minute canaliculi are

seen between the cells. Few large lacunae suggesting the former presence of fat globules are seen.

At 6 days, there are definite lacunae, and the cell outlines may not be distinguishable but the appearances are similar.

At 9 days, the cytoplasm is mossy or very finely granular and, though many small spaces are present, the appearance cannot so justly be described as foam-like. No large spaces indicating the former presence of fat globules are found.

Lymphatic glands.

At 3 days, two varieties of lymphatic glands are seen. In both endothelial cells predominate largely, but in one there is a fair admixture of plasma cells, in the other a few lymphocytes are found. Endothelial cells bearing blood pigment may be present or wanting. No nuclear débris is found.

At 6 days, the glands owing to acellularity show relatively much stromal connective tissue, the few cells present are mainly endothelial with perhaps some foci of plasma cells. Lymphocytes are very few. Usually no nuclear débris is found. Sometimes the vascularity is so great that haemolymph glands result.

At 9 days, the glands are highly acellular, possibly so vascular as to be of the haemolymph variety and contain endothelial cells, small mononuclear cells, very few lymphocytes. It is usual for pigment bearing endothelial cells to be present, but nuclear débris is not found.

Salivary gland.

At 3 days, the mucoid type of gland shows acini filled with cells having clear, swollen, faintly granular, mucoid cytoplasm, deeply stained, contracted, basally placed nuclei and well-marked membranes between contiguous cells. The serous type shows acini with finely basophil, granular cytoplasm intermingled with acini having finely oxyphil granular cytoplasm. The nuclei of the serous glands are round or oval, moderately stained and usually show dust-like chromatin. The ducts are lined by a layer of columnar cells having a conglomerate oxyphil hyaline cytoplasm and moderately stained nuclei in which is dust-like chromatin : the lumina of the ducts are empty.

At 6 days, the acini of mucous salivary gland are swollen but no differences are recognized in the serous type of gland or in the ducts.

At 9 days in the mucous salivary gland the cytoplasm is hyaline and granular or mucoid, and the nuclei are irregular or swollen, moderately and diffusely stained. In the serous type of gland acid foci appear to be more numerous, and the degree of oxyphilia to be greater ; the nuclei are irregular in shape and stain very deeply. In the ducts the nuclei are round, vesicular and stain faintly, but some particulate chromatin may be present.

C.   The combined effect of increased exposure and survival.

In this group the effects are largely intensified as being the sum of changes studied in the two preceding groups. Hence a

detailed description will not be given, but points of special importance alone will be noted.

The animals contained in group C are as follows :

Number.	Length of exposure.	Survival.
Q 10	5½ hours.	30 days (died after operation)
Q 5	12 ,,	2½ ,, died)
Q 12	16 ,.	2 ,, (killed)
Q 24	16 ..	3 ,, (killed)
Q 3	24 ..	2 ., (died)

Blood.

Q 10, which was exposed for 5½ hours and died 30 days later, showed numerous leucocytes. amongst which lymphocytes predominated largely.   Q 24 (16 hours' exposure, 3 days' survival) and Q 3 (24 hours' exposure, 2 days' survival) showed great disintegration of red blood corpuscles.

Striated muscle.

No special observations necessary.

Unstriated muscle.

No special observations necessary.

Cardiac muscle.

Q 12 (16 hours' exposure, 2 days' survival) and Q 3 (24 hours' exposure, 2 days' survival) showed much fragmentation of fibres ; Q 24 (16 hours' exposure, 3 days' survival) showed numerous ' ghost ' nuclei.

Endothelium.

No special observations necessary.

Liver.

In Q 10 (5½ hours' exposure, 30 days' survival) no necroses nor signs of inflammation were present, the hepatic cells and nuclei were normal in appearance. The stroma was somewhat cellular, and the nuclei within the bile ducts appeared to have undergone proliferation.   In the remaining animals of the group the hepatic substance frequently had a boiled appearance, ghost-like nuclei were very numerous, and many cells appeared to have lost their nuclei.   Much of the cytoplasm of the hepatic cells had become granular and disappeared and vacuolation was common. In frozen sections there was little evidence of lipoid or fat.

Spleen.

In Q 10 (5½ hours' exposure, 30 days' survival) the spleen represented ·074 c.c. per cm. of body length, many lymphocytes were present, few endothelial and few plasma cells.   The mean value of the spleen in the remaining animals of the group was ·016 per cm. of body length, there was much nuclear and red-corpuscular débris with great phagocytosis by the endothelial cells so that mulberry-like cells resulted.

Pancreas.

No special observations necessary.

Kidney.

In Q 10 (5½ hours' exposure, 30 days' survival) the convoluted tubules showed some disappearance of cytoplasm and numbers of 'ghost' nuclei, but the conducting tubules were apparently normal. In the remaining animals of the group the conducting tubules shared in the general great disorganization of the tissue. The pelvic epithelium shows a little irregularity and the nuclei tend to lie in lacunae but the differences are not marked. Frozen sections of Q 24 (16 hours' exposure, 3 days' survival) stained with Sudan showed fine lipoid deposit in the cells of the convoluted tubules, but this condition is abnormal in rats.

Adrenal.

In Q 10 (5½ hours' exposure, 30 days' survival) and Q 5 (12 hours' exposure, 2½ days' survival) vacuolation of the outer half of the cortical region represented the former presence of many large fat globules. In the remaining animals of the group there was less vacuolation, but rather a granular condition of the cytoplasm and the vacuoles themselves were small.

Stomach and intestines.

Beyond general intensification of the changes no special observations are necessary.

Generative system.

Testicle. No special observations necessary.

Ovary. In Q 10 (5½ hours' exposure, 30 days' survival) many large corpora lutea were present and numerous Graafian follicles of various sizes. The Graafian follicles showed degenerated cells and nuclear débris but no ovules were seen.

Lung.

No special observations necessary.

Thyroid.

In Q 24 (16 hours' exposure. 3 days' survival) frequently colloid had disappeared entirely from the vesicles.

Paraortic tissue.

No special observations necessary.

Lymphatic gland.

In Q 10 (5½ hours' exposure, 30 days' survival) the glands show great congestion, and some may be regarded as of the haemolymph gland variety. A certain amount of nuclear débris is present, but many lymphocytes and large pigment bearing endothelial cells are found. In other animals of the group acellularity is great, lymphocytes in particular being few. Though disintegration may, obviously, be imminent, little nuclear débris is found.

Salivary gland.

No special observations necessary.

HISTOLOGICAL AND SOME OTHER CHANGES IN THE RABBIT.

In this portion of the investigation 15 animals were subjected to the rays. Chief attention was directed to the question of survival, but the length of exposure was also considered. Although, in one group of animals, the exposure was for a single continuous period of 16 hours, whereas in another three exposures each of 16 hours were made on successive nights, all the animals will be considered together. In the last-mentioned group the effects noted are a complex of increased dosage and survival.

Rabbit number.	Length of exposure.	Survival.
Q 4	16 hours	Nil
Q 5	16 ,,	Nil
Q 6	16 ,,	3 days
Q 7	16 ,,	3 ..
Q 2	16 ..	6 ..
Q 3	16 ..	6 .,
Q 1	16 ,,	9 .,
Q 8	24 .,	9 ,,
Q 9	24 ..	9 ,,
Q 13	16 ..	16 .,
Q 14	16 .,	16 ..
Q 10	48 .,	Nil
Q 11	48 ,,	Nil
Q 12	48 ..	7 days (died)
Q 15	48 ..	7 ..

All animals were killed except Q 12. Q 15 was moribund when killed. Q 8 and Q 9, though exposed for 24 hours, are included in the group ; it is thought no real error is introduced thereby.

GENERAL SYMPTOMS DURING LIFE.

No symptoms of any kind were noted in the majority of animals, but rabbits, allowed to survive after a total exposure of 48 hours, became somnolent and, in one case, haemorrhage occurred from the ears. As will be seen later, haemorrhage is frequently noted in certain tissues.

Loss of weight was observed in 6 out of 7 animals, weighed before and after exposure. The loss varied between 135 gm. and 530 gm. in individual cases. In two animals (Q 13 and Q 14), exposed for 16 hours and allowed to survive 16 days, an initial loss of weight occurred but was made up during the second week of life after exposure.

There was no evidence of diarrhoea but, in more prolonged cases, there was impaired intestinal action and the faeces were ill-formed or loose.

Repeated blood examinations during life were made in 6 animals. In the case of red corpuscles, the end result was a diminution in number per c.mm., though a certain degree of polycythaemia might be noticeable as an early effect of the irradiation. The percentage of haemoglobin diminished but the colour index generally rose. In the case of leucocytes a

progressive leucopenia occurred due, essentially, to great destruc-
tion of lymphocytes. The number of polynuclear cells is increased
for a time, but the ultimate effect upon these cells depends upon
the intensity of the exposure; with prolonged exposure they
also suffer destruction. In Tables I and II are given figures
obtained in four rabbits exposed on each of three successive nights
for 16 hours.

TABLE I.   (RABBITS.)

Erythrocytes in millions per c.mm.

Rabbit.	Before irradiation.	After 1st exposure.	After 2nd exposure.	After 3rd exposure.	Remarks.
Q 10					
No.	6.50	5.00	5.60	4.70	Minimum im-
Hb per cent.	60	56	56	54	mediately after
Index	0.46	0.58	0.50	0.57	3rd exposure.
Q 11					
No.	9.1	8.46	7.68	6.94	Ditto.
Hb per cent.	66	59	77	67	,,
Index	0.37	0.44	0.52	0.41	,,
Q 12					
No.	8.34	8.28	9.3	7.34	,,
Hb per cent.	72	68	60	64	,,
Index	0.43	0.41	0.32	0.44	,,
Q 15					
No.	7.38	8.0	8.8	5.8	Minimum on
Hb per cent.	78	74	74	68	7th day after
Index	0.50	0.46	0.42	0.59	3rd exposure.

TABLE II.   (RABBITS.)

Absolute numbers of leucocytes per c.mm.

Rabbit.	Before irradiation.	After 1st exposure.	After 2nd exposure.	After 3rd exposure.	Remarks.
Q 10	13,600	37,200	18,600	2,400	Minimum im-
	L. 6,946	L. 5,022	L. 2,418	L. 504	mediately after
	P. 5,228	P. 27,216	P. 14,432	P. 1,884	3rd exposure.
Q 11	5,900	6,050	5,600	2,700	Ditto.
	L. 3,658	L. 1,119	L. 784	L. 392	,,
	P. 885	P. 3,710	P. 4,812	P. 1,849	,,
Q 12	6,400	10,400	5,900	3,900	,,
	L. 2,752	L. 520	L. 354	L. 119	,,
	P. 1,088	P. 9,464	P. 5,487	P. 3,607	..
Q 15	9,600	4,500	4,000	3,200	Minimum on
	L. 5,904	L. 45	L. 400	L. 128	5th day after
	P. 2,496	P. 4,363	P. 3,440	P. 3,040	exposure.

L = Lymphocytes.
P = Polynuclear cells.

The other varieties of leucocytes behave in approximately
the same fashion. In all examinations of circulating blood
nucleated red blood corpuscles have been conspicuously absent.

POST-MORTEM APPEARANCES.

In all the animals one of the most noticeable features was the
relatively small size of the spleen. In a normal rabbit spleen

constituted 0·079 c.c. per cm. of length, but, in the entire series
of 15 irradiated rabbits, the mean was 0·0143 c.c. per cm. of
length with maximum of 0·03 c.c. and minimum of 0·006 c.c.
Reference is made to this point on p. 110.   Corresponding with
the alteration of spleen and the changes of circulating blood,
noted above, changes were found in bone-marrow.   Usually,
medulla of femur was deep red or mottled and very soft ; tibial
medulla was less affected, and the lower end might be yellow
whereas the upper end was pink and mottled.   So far as other
post-mortem changes were concerned, even after a total exposure
of 48 hours, nothing might be considered noteworthy if the
animal were killed immediately after exposure, though the
stomach and intestines might be highly distended, and some
haemorrhage might have occurred.   But, if such an animal were
allowed to survive for 7 days, haemorrhages were found in the
muscle, and beneath the serous and mucous membranes, while
frequently much mucus filled the intestine.   With prolonged
survival similar post-mortem appearances were found to follow a
single exposure of 16 hours.

MICROSCOPICAL APPEARANCES.

Blood.

    After a single exposure of 16 hours no marked changes are
seen in the appearances of red blood corpuscles within the blood-
vessels ; they may be discrete or form a conglomerate homo-
geneous mass, and usually stain fairly well.   On the other hand,
a total exposure of 48 hours, or relatively prolonged survival
after a shorter exposure, leads to the appearances of non-cellular
thrombus within the vessels, and staining of erythrocytes is
poor.   A single exposure of 16 hours sometimes leads to small
haemorrhages in the tissues.   Considerable extravasations follow
a total exposure of 48 hours.
    After an exposure very few leucocytes are seen, and the
degree of their immediate disappearance does not greatly differ
according as the exposure has been 16 hours or 48 hours.   Such
cells as are found are almost invariably polynuclear in which the
nuclear staining is abnormally intense or abnormally faint.   With
an exposure of 48 hours there is no return of leucocytes during
the remaining 6 or 7 days of survival, but after the 9th day,
following a single exposure of 16 hours, there is some tendency
to recovery of leucocyte numbers, and the principal feature is a
reappearance of lymphocytes.   Although the total number of
leucocytes per c.mm. may still be low, lymphocytes predominate
largely.

Striated Muscle.

    The contractile material of abdominal muscle presents a fairly
uniform appearance throughout the entire series.   The muscle
fibres are generally swollen, hyaline, or cloudy, present faint or
fair striation, very rarely show the translucent change, and,
though occasionally they may be irregular, or easily broken down,

or split transversely, they rarely show vacuolation. It is not possible to associate any particular appearances of the contractile material with length of exposure or survival of the animal. The nuclei vary in shape and amount of particulate chromatin. With regard to the former it is impossible to speak with certainty, but rough measurements have shown that the ratio of length to breadth of the muscle nucleus diminishes with survival after exposure up to about the 9th day and then increases. Thus, in animals killed immediately after an exposure of 16 hours, the ratio length-breadth was found to be about 7; after 3 days' survival it was about 6, after 6 days' survival about $3\frac{1}{2}$, after 9 days' survival about $3\frac{1}{2}$, and after 16 days' survival it had returned to and surpassed normal and was about $7\frac{1}{2}$. Animals exposed on 3 successive nights for 16 hours do not show this relative swelling of nuclei in abdominal muscle, but the ratio length-breadth is 8 for animals killed immediately after exposure and 9 for those surviving for 7 days. In the normal rabbit the length of nuclei of abdominal muscle and biceps averages $6\frac{1}{2}$ times the breadth. No definite 'ghosts' nor other degenerate forms are seen with certainty. The intermuscular spaces present no special features.

In bicipital muscle the contractile material shows less swelling, is less frequently hyaline or cloudy, but is more frequently fibrillated and more often shows translucency of some of the fibres. Striation is better than in abdominal muscle. The nuclei vary in depth of staining, but usually stain faintly or moderately and show a little particulate chromatin. 'Ghosts' and degenerate forms are rarely seen. The ratio length-breadth of nuclei in bicipital muscle runs a similar course to that found for abdominal muscle. Thus in animals killed immediately after an exposure of 16 hours it was found to be about $5\frac{1}{4}$, after 3 days' survival about $4\frac{1}{4}$, after 6 days' survival about 5, after 9 days' survival about $4\frac{1}{2}$, and after 16 days' survival it was about $7\frac{1}{4}$.

A few specimens of thoracic muscle were taken, but add little to the above description.

Frozen sections stained with Sudan show many fibres that take the dye, but lipoid globules are rare.

Unstriated Muscle.

In stomach the contractile material is hyaline, and usually somewhat fibrillated. Vacuolation is generally present in some degree and occasionally is marked; it appears to be more evident immediately after exposure and in the early days of survival. The reaction is generally acid. The nuclei are very irregular in shape and staining, but commonly are long and sinuous or contorted rods, faintly and diffusely stained. Vacuolated or vesicular forms are frequently seen, and occasionally longitudinal splitting or swollen forms occur. Irregular distribution of chromatin in the nucleus is common, discrete particles are unusual.

In duodenum the contractile material is scanty, hyaline, fibrillated, often shows clefts and sometimes vacuoles. Staining is uneven and may be basophil or neutral, rarely it is slightly

oxyphil. The muscle appears to undergo fragmentation with ease. The nuclei are irregular in shape, being long, sinuous, short, thick or swollen, and staining is generally faint and diffuse. Nuclear vacuolation is usually present.

In jejunum the contractile material is scanty, hyaline, fibrillated, occasionally shows vacuoles or clefts, is sometimes swollen or fragmented, staining is neutral or faintly oxyphil, less commonly faintly basophil. The nuclei are usually long and sinuous or irregular in shape, faintly and diffusely or irregularly stained, and a certain amount of nuclear vacuolation is generally present, though it is less pronounced than in duodenum.

In ileum the contractile material is hyaline and fibrillated, often swollen and semi-translucent, may show vacuolation or clefts, and the staining is usually oxyphil. The nuclei are usually swollen and vacuolated, and sometimes the changes are pronounced. The shape is irregular and staining is usually poor or faint and diffuse. Particulate chromatin is not found, but the distribution of the chromatin in the nucleus is often very irregular.

In colon the contractile material is hyaline and slightly fibrillar, but staining is uneven and poor. Clefts are frequently seen, vacuolation sometimes. As a rule the staining is oxyphil, but it may be neutral or basophil. The nuclei are irregular in shape, often are swollen and vacuolated or vesicular. Staining is faint and diffuse, as a rule with irregular distribution of chromatin; particulate chromatin is very uncommon.

In rectum the contractile material is hyaline and fibrillar, frequently shows clefts, but vacuolation is uncommon. Usually the staining is oxyphil, but is not conspicuously uneven. The nuclei are often swollen and generally vacuolated, staining is faint and diffuse or irregular. Occasionally 'ghosts' are seen.

In artery the contractile material is hyaline and rarely fibrillar, vacuoles are numerous particularly in the aorta and large vessels. In the arterioles the contractile substance is semi-translucent and vacuoles are not found. Staining is usually basophil. The nuclei are frequently swollen and stain faintly and diffusely but irregular forms are often seen. Vacuolation is common except in the nuclei of arterioles.

Over the whole range of situations it appears that swelling and vacuolation of contractile material and of nuclei is particularly associated with length of survival or length of exposure.

Cardiac Muscle.

The muscle-fibres show a hyaline, finely granular, contractile material in which there is very poor striation, or striation may be wanting. Sometimes there is fibrillation of the bundles. In cases of relatively long survival after exposure, fragmentation, vacuolation, and translucency of the bundles may occur, and the intermuscular spaces are wide though empty. When the length of exposure has been very great, the intermuscular spaces contain coagulated albumin or perhaps red blood corpuscles, and, in such cases, subserous petechial haemorrhages occur. The nuclei vary

in appearance, but frequently are irregular in shape and vacuo-
lated or swollen or vesicular. The length may be roughly 3-4
times the width, but frequently it is not more than twice. In
the normal rabbit the length of cardiac muscle nuclei averages
5⅓ times the breadth. Nuclear staining is faint, but a little dust-
like chromatin may be present. More commonly the staining is
irregular owing to vacuolation of the nucleus and irregular
distribution of the chromatin. As an immediate or recent effect
of exposure an even nuclear swelling appears to result, and this
is most marked with the heaviest dosage. A later effect of
survival is seen in the occurrence of nuclear vacuolation and
irregularity of shape and staining.

Connective Tissue.

No noteworthy features attach to the nuclei. They are few
in number and either deeply stained and contracted (connective
tissue cells) or are the diffusely stained nuclei of included
endothelial cells. No adventitious cells are present. In dense
fibrous tissue the fibrils are glassy, collagenous or swollen, and in
the loose variety they are swollen or gelatinous in animals killed
immediately after exposure or in the early days of survival. But
after about the 9th day of survival, after exposure for 16 hours,
these appearances are lost to a great extent and the fibres become
sharply defined and delicate.

Endothelium.

Over the gastro-intestinal tract the endothelium is poor on
the whole, though the appearances differ in different regions.
Of the 15 animals a 'fair endothelium or better' was found over
stomach in 5, over duodenum in 4, over jejunum in 6, and over
ileum, colon, and rectum in 7. In the remaining instances the
endothelium was 'shreddy' or 'detached' or 'disintegrating', or
'traces' alone were present. Often the cytoplasm was more
intensely stained than normal. The nuclei varied greatly, being
linear, lenticular, or irregular in shape, and intensely stained, or
round, oval, or vesicular and faintly stained. In either instance
staining was diffuse. The only safe conclusions are, that the
condition of endothelium was worst over the duodenum and best
over the large intestine, and that a great readiness towards
desquamation and degeneration was manifest in all cases. These
experiments do not indicate a special influence on endothelium of
survival after exposure or increased length of exposure.

Over spleen a fair endothelium or better was present in 11
instances, but the nuclei frequently were vesicular and varied
much in depth of staining. Within the substance of the organ
the nuclei of endothelial cells were generally irregular in shape,
vesicular, and faintly stained. The cytoplasm was hyaline and
conglomerate, but, in some instances, isolated cells were present
which carried large quantities of broken-down erythrocytic
material or pigment. In lung little desquamation was seen, and
the endothelium calls for no special remark. In large and small
blood-vessels a good endothelial lining is found with great con-

stancy. The nuclei generally stain intensely and diffusely, but, in cases in which the exposure has lasted for 48 hours in all, the nuclei are often irregular in shape.

In none of the regions over which the condition of the endo-thelium has been examined has the slightest trace of prolifera-tion been observed.

Liver.

The tissue in general is coherent and shows no special conges-tion though the larger vessels contain blood and the capillaries are widely dilated. Such blood as is present is partially broken down and amorphous débris may be found in the capillaries. The hepatic cells show a swollen, cloudy or hyaline, ill-defined cytoplasm with little granularity in animals killed immediately after exposure, but granules are formed at the expense of the cytoplasm in the early days of survival and rapidly disappear. Hence by the 9th day after an exposure for 16 hours, the cyto-plasm of the cells may be represented by a few ill-formed granular masses alone. The cytoplasm may show a few lacunae, the former situation of fat globules, but vacuolation of the cyto-plasm itself hardly occurs. The nuclei of hepatic cells when least altered, are round, sharply defined, contain little chromatin, but usually present a nucleolus. Though such nuclei are to be found in most specimens, ' ghosts ' and other degenerative forms are frequently met with. These degenerative forms may take any shape from (i) a ' ghost ' (which differs from the normal nucleus only by its poor definition), through (ii) a condition in which the nucleus is represented by a constellation of chromatin points with the size and shape of a nucleus, but without nuclear membrane, and (iii) a condition in which a minute collection of chromatin lies within the cell, to (iv) one in which no trace of nucleus is visible in the cytoplasm. Where such degenerative changes are pronounced, nuclear débris is often present in rela-tively large quantity. In animals where survival after exposure is prolonged, paired or twin nuclei are often seen in the hepatic cells. These nuclei are smaller than single nuclei, are in appo-sition or placed close together, and are identical in appearance as a rule. In other respects, they resemble the nuclei usually found. A curious appearance of the liver cells is that in which exten-sive disappearance of cytoplasm has occurred. In these cases a sponge-like tissue results from persistence of the cell-membranes alone, and though many of the nuclei may have disappeared, some remain within the cells. In such cases the nuclei are swollen, present an irregular outline, and are deeply and dif-fusely stained. As indicated above, this condition is a late result of the exposure to irradiations. The bile ducts lie in a definite fibrous tissue sheath and are lined by a low columnar epithelium with hyaline cytoplasm and oval, very faintly stained nuclei. The lumen of the ducts is usually small and the lining epithelium may be swollen. Occasionally there is complete occlusion.

In frozen sections stained with Sudan or osmic acid or Nile

blue very little evidence of lipoid or fat is found. The appear-
ances cannot be associated with conditions of survival or exposure.
No changes have been noted in the characters of Glisson's capsule
and its prolongations. Pigment is rarely found in the cells, and,
in spite of the great destruction of red blood corpuscles, there is
no evidence of siderosis.

Spleen.

Reference has already been made to diminution in the size
of the organ and to the appearances of the endothelial cells on
the surface and within the spleen pulp. The cohesion of the
tissue is generally good. Malpighian corpuscles are very few
and poorly defined in animals subjected to a single exposure of
16 hours, and killed immediately or allowed to survive for 3 days.
But at 6 days' survival there is a little improvement, at 9 days
the Malpighian corpuscles are fair, and at 16 days they are good.
In the case of animals subjected, on 3 successive nights, to an
exposure of 16 hours, Malpighian corpuscles are hardly distin-
guishable, whether the animal be killed immediately after the
exposure or have been allowed to survive 7 days. As a result of
the relative disappearance of the Malpighian corpuscles, the
spleen pulp becomes highly acellular except for the presence of
red blood corpuscles. The cells present are mainly endothelial
with an admixture of some small mononuclear cells, and occa-
sionally a few plasma cells. In pronounced cases, lymphocytes
have disappeared almost entirely, but, when the tissue is less
acellular, a differentiation between lymphocytes and small
mononuclear cells is made with difficulty. Masses of lympho-
cytic nuclei undergoing disintegration or of definite nuclear
débris are frequently seen immediately after exposure and persist
for a few days, but by the 6th day of survival the greater part
has disappeared, and by the 9th and 16th days a careful search
will reveal no more than traces. In contrast to the free nuclear
débris, endothelial cells containing corpuscular or blood pigment
débris are more numerous at about the 9th day of survival after
a single irradiation of 16 hours. With a total exposure of 48
hours, these macrophages are numerous, whether the animal be
killed immediately after exposure or be allowed to survive
7 days. The stroma seems to consist chiefly of the conglomerate
hyaline cytoplasm of endothelial cells ; there is little evidence
of connective tissue, but small trabeculae of unstriped muscle are
present.

Pancreas.

In tissue from animals killed immediately after an exposure
of 16 hours, the acini are well formed, though clefts may be
present. The pancreatic cells are swollen and hyaline, oxyphil
at the centre of the acinus, basophil peripherally, and the nuclei
are vesicular and faintly stained. The ducts are lined by a layer
of swollen columnar epithelium, with vesicular, poorly stained
nuclei, and a plug of mucus may obstruct the lumen. The
islands of Langerhans are rather difficult to distinguish, show

a conglomerate hyaline cytoplasm and small, round, moderately stained nuclei. On the whole, definition is good. As survival lengthens after exposure up to the 9th day, the condition of the pancreatic cells deteriorates. The cytoplasm is neutral or basophil throughout, or any central oxyphilia is very poor and a swollen or parboiled condition is often present. The nuclei are vesicular or faintly stained, and 'ghosts' become numerous. The ducts show no important differences, but no plug of mucus is present in the lumen. The islands of Langerhans vary, but often are very difficult to distinguish. At 16 days' survival the appearances are better ; central oxyphilia and peripheral basophilia of the acini is found, the nuclei are less vesicular, and islands of Langerhans are well marked. In animals subjected for each of three successive nights to an exposure of 16 hours, the cytoplasm is cloudy, poorly stained, sometimes undergoes mucoid degeneration, and shows clefts, while many of the nuclei are vesicular and faintly stained or irregular and deeply stained, and many 'ghosts' are present.

Kidney.

The organ is generally more or less congested and small haemorrhages are found with some frequency. The glomerular tufts are contracted, but patent capillaries are common. The endothelium lining Bowman's capsule is well preserved, the nuclei being linear and staining intensely ; endothelial nuclei found on the tuft itself vary greatly in size, shape, and staining. The glomerular space is usually small and empty, but a few red blood corpuscles or a little amorphous albuminous material may be present in some of the glomeruli. In animals allowed to survive after a total exposure of 48 hours the glomerular tufts appear to be swollen, few capillaries are visible, the tuft may be composed in part of homogeneous, coagulated albumin, and the glomerular space is narrow. In such cases, small haemorrhages into the cortex of the kidney are numerous.

The convoluted tubules usually show a narrow irregular lumen, but sometimes, owing to swelling of the renal cells, the lumen may be reduced to a mere cleft, and, at other times, it may be wide owing to disintegration of the inner portions of the cells. In the latter instance, the lumen contains albuminous débris, or may be bridged by strands of coagulum. The renal cells are hyaline or very occasionally granular, basal striation is rarely present, and often the inner portion of the cell has disintegrated, leaving the nucleus exposed. Apart from separation of the cells and disintegration of the cytoplasm (which appears to be more pronounced with survival), the chief change is in the nuclei. When these are well preserved they are round, even in size, faintly stained, often nucleolated, and show a small amount of dust-like chromatin. But a general feature of the entire series is the presence of 'ghosts' and forms even more degenerated. In the case of animals exposed for a single period of 16 hours, the number of 'ghosts' is at its maximum immediately after exposure and decreases as the period of survival lengthens. On

the other hand, small groups of mere chromatin points without nuclear membrane and cytoplasm devoid of nuclei progressively become more noticeable as the period of survival lengthens up to the 9th day. Subsequent to about the 9th day, the condition of the renal epithelium may improve or deteriorate considerably. In rabbits exposed for 48 hours the changes described above are intensified.

In the conducting tubules the cytoplasm of the lining cells is usually translucent and scanty or has disappeared entirely, leaving the cell to be represented by a naked nucleus within a cell membrane. Sometimes the cells are swollen immediately after exposure, but with survival there is a progressive disintegration and desquamation or that disappearance of cytoplasm to which reference has been made. As a rule the nuclei are vesicular, sharply defined, faintly stained, and show a little particulate chromatin or a nucleolus. In tubules close to the tip of the papilla casts may be present. These are hyaline or granular or may contain free nuclei or a little blood, but epithelial casts are not found. Otherwise the lumina of tubules are wide and empty, or at most contain a little amorphous material.

The stroma of the kidney, the blood-vessels, and the epithelial lining of the pelvis call for no special remark.

Frozen sections stained with Sudan or osmic acid or Nile blue show no trace of lipoid or neutral fat. The utmost that obtains is that the epithelium of the convoluted tubules takes a little more Sudan stain than the rest of the section.

Adrenal.

The zona glomerulosa is usually well marked but sometimes is difficult to distinguish from the cortex. The cells are small and tend to be arranged in columns. The cytoplasm is rather scanty, finely granular, and the nuclei are fairly well defined and closely packed. In the cortex the cells are larger, and, over the outer half, the outlines are usually fairly distinct and the cytoplasm is scanty, finely granular, or finely foam-like. Lacunae, the former seat of fat globules, are very infrequent. The cytoplasm appears to be scanty and granular shortly after exposure and to become more hyaline and voluminous with survival. Occasionally the cytoplasm disappears entirely and the cell is represented by nucleus and cell membrane alone. The nuclei of the cortical cells are small, round, stain moderately and diffusely, but may show a nucleolus. 'Ghosts' are occasionally present immediately after a single exposure of 16 hours, but their numbers increase with survival. With total exposures of 48 hours and subsequent survival, 'ghosts' and still more degenerated nuclear forms are common. As a rule they are not found in the zona glomerulosa nor in the inner portion of the cortex, but in advanced cases they are present in these regions also. The medulla shows an ill-defined alveolar arrangement with large blood sinuses, the cytoplasm is conglomerate, scanty, and finely granular, the nuclei are large, vesicular, and often show a nucleolus or a little particulate chromatin. No differences

have been detected in the medulla with survival or excessive exposure.

Stomach and Intestines.

Towards the cardiac end of the stomach the mucosa is of even thickness and consists of tubular glands closely packed and with little intervening connective tissue. The investing layer has disappeared in the great majority of cases. The tubules contain two varieties of cells: (*a*) large cells with clear, non-granular, oxyphil cytoplasm and small vesicular nuclei, and (*b*) swollen, ill-defined cells with relatively little granular basophil cytoplasm and small, ill-defined nuclei. The latter cells are found chiefly towards the blind ends of the tubules, but are intermingled to a small extent with the oxyphil cells. Towards the orifice of the tubules, oxyphil cells alone are present and show a variable degree of degeneration or desquamation. Generally, the epithelium in these tubules persists, but is much swollen, and the nuclei are vesicular. With survival after exposure the appearances differ widely; in some cases desquamation and mucoid degeneration are pronounced, in others the condition of the mucosa is fair. In animals killed after a total exposure of 48 hours there is great swelling, much mucus, the lumina of the tubular glands are obliterated by accumulated mucus and desquamated cells and haemorrhages may be present. 'Ghost' nuclei are occasionally seen.

Towards the pyloric end the mucosa is villous and the appearances are more irregular, but resemble those found in the cardiac region. The tubules vary much in length, and the greater part of the epithelium has desquamated in many instances. The oxyphil and basophil types of cells are present. Mucus and mucoid degeneration of the cells are marked features. Doubtful mitotic figures were found in animals surviving 16 days after a single exposure of 16 hours, but in no other group of the series. The stroma is scanty in animals killed immediately after a single exposure or in those that have survived 9 days or longer, but is swollen, gelatinous, or mucoid under other conditions.

Duodenum. Brunner's glands are well preserved and show no clear differences under variations of experiment. In all cases the mucoid change is intense. Great degenerative changes are present in the investing epithelium and that lining the tubular glands. The investing epithelium is partly or entirely desquamated, and the degeneration appears to become more marked up to about the 6th day of survival. From the 9th day onwards the condition is not so severe. The epithelium lining the tubular glands is usually present in part, but the cells are often loosened, and, towards the orifices of the glands, desquamation may have occurred. Immediately after a single exposure of 16 hours, the staining of the cells is poor, the nuclei are vesicular, goblet cells are many, though actual mucus is scanty, and mitoses are absent. At the 6th day of survival disintegration of cells is increased, goblet cells become fewer, but mucoid degeneration of epithelium and mucus increase in quantity and deformed mitotic figures make their appearance

By the 9th day deformed mitoses are numerous, and in a few cases the condition of the mucosa appears to improve, but in the majority it becomes impaired still further, so that, by the 16th day, there is great desquamation and mucoid degeneration, and few mitoses are seen. The stroma is usually scanty in the early days of survival, but becomes voluminous and oedematous by about the 9th day. Cells may be present in considerable numbers and are usually endothelial, small mononuclear, and sometimes plasma cells, but polynuclear leucocytes are not found. In the later days of survival the desquamation is such that the stroma is sometimes denuded of epithelium. After three exposures of 16 hours on successive nights, the appearances are intensified, but desquamation is not always marked, although intense mucoid degeneration of the epithelium may be present.

Jejunum. The mucosal changes resemble those in duodenum, but are intensified. In some cases nuclear débris is present in the blind ends of the tubular glands. Frequently remnants of tubular glands alone are left. In animals surviving 7 days after a total exposure of 48 hours, oedema of the submucosal connective tissue is marked.

Ileum. The changes in mucosa of ileum resemble those in duodenum and jejunum. Occasionally the condition is worse, usually it is somewhat less advanced. Goblet cells are numerous up to the 3rd day of survival after a single exposure, but are less common subsequently, though there may be mucoid degeneration of the columnar epithelium. During this period a large amount of nuclear débris is found in the tubules. A few deformed mitoses are seen in specimens from the 3rd to the 16th days of survival after a single exposure.

Colon. The investing columnar epithelium is fairly preserved, and in cases of survival for 9 and 16 days after a single exposure of 16 hours it is good. In animals exposed for 48 hours in all, the investing epithelium persists, but is the seat of intense mucoid degeneration, the cells being swollen and the nuclei vesicular. Goblet cells are relatively few, but there is a considerable formation of mucus as seen by the free mucus in the lumen of the gut and the mucoid degeneration of the epithelial cells. Some definite oval foci of deeply stained mucoid or colloid material are seen in the investing epithelium or that lining the tubular glands. More rarely such foci occur in ileum, jejunum, or duodenum. The stroma is scanty and frequently is oedematous; it contains few cells. An occasional mitosis has been found in animals surviving 3, 6, and 9 days after a single exposure of 16 hours.

Rectum. The investing epithelium is well preserved. The tubular glands are short and wide; the epithelium has undergone marked mucoid change; and oval, deeply stained, mucoid or colloid foci are very numerous. Goblet cells and mitotic figures are rare or absent. The stroma is oedematous or gelatinous and varies in quantity. It is rarely cellular and such cells as are present are usually endothelial or small mononuclear, with, perhaps, a few plasma cells.

In six animals (Nos 5, 6, 7, 8, 9, 10) a certain degree of compli-

cation was noticed by the presence of intestinal parasites. How far the mucoid changes of the secretory epithelium and the cellular condition of the stroma were influenced thereby is uncertain.

Generative System.

The testicle shows some contraction of the tubules, but the normal cellular contents are present. Cells of Sertoli are few and ill-defined ; spermatogonia and spermatocytes are generally present ; spermatoblasts are fewer and less constant and spermatids are not usually seen in specimens taken immediately after, or 3 days after exposure, but at 9 and 16 days they are found with fair regularity. Spermatozoa are unusual in the tubules. The spermatogonia and spermatocytes of the first order are often in prophase ; no diaster forms are seen. The mitotic figures are intensely basophil, but there is lack of sharpness. In the epididymis the tubules are lined by a well preserved ciliated epithelium and the lumen generally contains partially broken down spermatozoa and cell débris. The various specimens do not differ very widely in the degree of degeneration recognizable in spite of differences in survival and of length of exposure. In most instances the heads of spermatozoa are intensely basophil, but occasionally staining is neutral or even oxyphil; the last-mentioned condition may occur within the seminal tubules but is common in the epididymis. Many of the nuclei of spermatocytes are vesicular and occasionally the cytoplasm of spermatogonia has disappeared, leaving the nucleus naked within the cell membrane. The stroma of the organ is always scanty and consists of a vascular connective tissue in which a few endothelial cells are present.

Ovary. The endothelial covering is well preserved and the stroma is scanty. In animals killed immediately, or surviving 6 days, Graafian follicles and ovules are numerous, and corpora lutea may or may not be present. The follicles show irregular arrangement of cells, while the cytoplasm of the cells themselves is breaking down and their nuclei are ill-defined and stain faintly. In smaller follicles and ovules a small, irregular mass of colourless coagulum alone is present. In the corpora lutea the cells vary widely in character, but preservation is good. Few differences from the above are noted when the total exposure has been 48 hours if the animal has been killed immediately, but if it has survived 7 days, Graafian follicles and ovules are few and represented by little more than structureless coagulum, or haemorrhages of considerable size may have occurred in the follicles.

In all cases the interstitial gland substance is evident and sometimes it is remarkable by the quantity present and its great similarity to cortical substance of adrenal or paraortic tissue of rat. The Fallopian tube shows a polypose or plicated lining of endometrial type. The cells are irregularly columnar in shape and the nuclei are vesicular and stain poorly.

Lung.

The lung shows alternating areas of compression or collapse and emphysema. The alveolar spaces are practically empty,

though a few desquamated endothelial cells or red blood corpuscles, or a little albuminous material may be found occasionally. The bronchi show a moderately well-marked columnar epithelium which may be ciliated. There is no evidence of mucus formation, goblet cells are wanting, but the cells may be swollen and appear on the verge of desquamation. A little amorphous granular material may be found in the lumen but there is no excess of mucus. No special features can be associated with survival or with increased length of exposure.

Thyroid.

The acini of the thyroid vary much in size, but they agree in containing colloid in the great majority of instances. Nevertheless there is often a central vacuolation of the colloid and, rarely, it has completely disappeared from some of the acini. The epithelium is cuboidal and the cytoplasm is scanty. The nuclei are vesicular and a few 'ghosts' may be present in animals killed immediately after a single exposure of 16 hours or those that have survived. After a total exposure of 48 hours many 'ghosts' are found, particularly if the animal has survived for 7 days. Under these conditions also there is probably a greater disappearance of colloid but, on this point, it is difficult to be certain. The interstitial substance often contains extravasated blood, but it is probable that this depends, in part at least, upon the manner of killing the animal.

Parathyroid.

Only four specimens are available. In the case of an animal living 7 days after a total exposure of 48 hours, the nuclei were swollen, stained faintly and showed a little dust-like chromatin, whereas in all other specimens staining was moderate and diffuse.

Lymphatic Gland.

The appearances differ somewhat in different glands, but generally there is a great degree of patchy acellularity concerning chiefly the lymphocytes. Nevertheless some lymphocytes are always to be found. In an animal killed immediately after a single exposure of 16 hours some nuclear débris was present, but in survivors at 16 days none was found. Similarly, in an animal killed immediately after a total exposure of 48 hours, the lymphatic glands showed a little nuclear débris, but in survivors at 7 days no débris was present. On the other hand large endothelial cells crammed with the débris of red blood corpuscles were common in survivors but absent from animals killed immediately after exposure. The endothelial cells do not disappear in the same way as the lymphocytes, and large germinal areas composed entirely of endothelial cells with perhaps some foci of plasma cells make up the greater part of the gland tissue. The glands are usually somewhat vascular and may be intensely so.

Salivary Gland.

In the majority of cases two varieties of acini are recognized (*a*) with basophil granules (*b*) relatively agranular and oxyphil. These two varieties are intermingled in the same lobule. The tissue is generally well-preserved, and the only differences that have been observed with survival are occasional elimination of oxyphil acini, the presence of ghost-like nuclei and the occlusion of ducts by a mucous plug. After an exposure amounting to 48 hours early mucoid change may be so pronounced that the cell membranes become conspicuous, and the columnar cells of the salivary ducts may be swollen, but otherwise no differences from the above were noted.

Bone-marrow.

The changes in bone-marrow are the subject of a special report by Dr. Price Jones. Here it may be noted that haemorrhages were a conspicuous feature of every specimen, that multinucleated cells diminished in numbers after the third day of survival and did not recover, whereas the diminution in numbers of the other varieties of nucleated cells tended to recover, that nuclear débris was sometimes found in tibial medulla, that fewer cells were present in tibial than in femoral medulla, but that otherwise the appearances were identical.

In animals exposed for a total period of 48 hours the appearances were intensified, few multinucleated cells were found in rabbits killed immediately after exposure, and none in those surviving for 7 days. Much of the blood in the haemorrhages was undergoing disintegration.

HISTOLOGICAL AND SOME OTHER CHANGES IN THE CAT.

In this portion of the investigation, 9 animals were subjected to the rays. Chief attention was directed to the effect of survival after a considerable exposure. The length of exposure and of survival were as follows :

No. of animal.	Length of exposure.	Survival.		
Cat QH	24 hours	Living		
QD	24 ,,	Died 12 days later		
QG	30 ,,	,,	14 ,,	,,
QB	36 ,,	,,	6 ,,	,,
QI	48 ,,	,,	5 ,,	,,
QC	64 ,,	,,	11 ,,	,,
QF	90 ,,	,,	2 ,,	,,
QE	95 ,,	,,	4 ,,	,,
QA	96 ,,	,,	under radium	

Symptoms during Life.

During the exposure itself and for the first day or two of survival nothing unusual was noted but, at some period bearing a relation to the length of exposure, the animal refused food and

became somnolent.   Mucus might exude from the mouth or the anus and there might be definite diarrhoea.

In two animals where the point was noted, the hair began to fall out on the 6th day after an exposure of 64 hours (back of Cat QC), on the 9th day after an exposure of 24 hours (back of Cat QD), on the 14th day after an exposure of 6 hours (flank of Cat QD). In one animal (QA, 96 hours) there was bloody discharge from the mouth, one animal (QF, 90 hours) showed twitchings and convulsions, and one cat (QC) aborted.   The one cat that survived (QH, 24 hours) subsequently had two litters of kittens.   In one animal (Cat QC, 64 hours) blood examinations were made for comparison with those carried out on rabbits.   Before exposure the erythrocytes were (in millions) 6·4 per c.mm. after the first exposure 6·5, after the second 6·6, after the third 8·8.   The haemoglobin index fell from 0·56 to 0·40.   Leucocytes before exposure were (in thousands) 14·2, after the first exposure 11·8, after the second 2·4, after the third 1·7.   The lymphocytes underwent a diminution per c.mm. from 2,556 to 413 and ultimately to 204.   The polynuclear cells rose slightly at first (from 10,650 to 11,269) but, after the second exposure, fell to 1,920 and, after the third, to 1,420.   Large mononuclear and eosinophil cells showed similar falls.

POST-MORTEM APPEARANCES.

Haemorrhage and extravasation were present in marked degree in four of the eight cases that died.   It was found in the gastric mucosa, lymphatic glands, mesentery, urinary bladder.   Mucus in great quantity was common in the colon and rectum but might also be found in the small intestine and stomach, and in the trachea.   The stomach was often much distended.   The spleen varied considerably in size, the maximum being 0·26 c.cm. per cm. of length and the minimum 0·071 c.cm.   The mean value per cm. of length in the radiated cats was 0·135 c.cm.   In a normal animal it was ·097.

In one cat in which the bone-marrow was examined it was intensely haemorrhagic.

MICROSCOPICAL APPEARANCES.

Blood.

The red blood corpuscles within the blood-vessels were usually well formed, and discrete, but degenerate forms were often seen in the liver, and numerous endothelial cells crammed with corpuscular débris were found in spleen and lymphatic glands.   Noncorpuscular thrombus was often present in the vessels and sometimes fibrin filaments were visible.   In some animals there were many small extravasations.   Leucocytes were very seldom seen.

Striated Muscle.

In abdominal muscle striation is very poor and frequently wanting, the contractile material is swollen and translucent, while staining is often patchy, and a small amount of amorphous albuminous material lies on the fibres.   The intermuscular space is

often wide and contains a little albuminous material but no adventitious cells are present. The nuclei are faintly stained rods, few in number, and may be recognizable only with difficulty. The ratio length : breadth (normal cat $3\frac{1}{3}$: 1) varies but is about 12 : 1 with exposures of 48 hours or less, about 8 : 1 with longer exposures. A little particulate chromatin or a nucleolus is often seen but deeply and diffusely stained or vacuolated forms are not very uncommon.

In bicipital muscle striation is very scanty and poor. The contractile material shows less translucency than abdominal muscle but is hyaline and swollen or sometimes granular. Staining is somewhat patchy. The intermuscular spaces are wide and contain a little granular albuminous deposit but no adventitious cells. The nuclei are faintly stained as a rule and the length is roughly 5–6 times the breadth (normal cat 3 : 1). They may be irregularly and diffusely stained or show a little particulate chromatin.

In one case (Cat QG, 30 hours) vertebral muscle from the back of the abdominal cavity and muscle of abdominal wall were subjected to identical and simultaneous processes with the object of instituting a comparison. Obviously the vertebral muscle had received a greater amount of irradiation owing to its nearness to the radium. The vertebral muscle was hyaline, showed little striation though striation was excellent in a few fibres. Few nuclei were seen; they were deeply stained but showed some particulate chromatin. The abdominal muscle was hyaline, showed no striation and was apparently a little more oxyphil than vertebral muscle. The nuclei stained moderately deeply, showed some particulate chromatin, and were on the whole wider than nuclei of vertebral muscle.

In frozen sections, stained with Sudan, striation varies widely but some degree is always found. Many fibres are translucent. Staining of some of the fibres and fine lipoid deposit are present in cases in which exposure was shorter and survival longer, and was absent where exposure was longer and survival shorter.

Unstriated Muscle.

In *stomach* the contractile material is generally hyaline, swollen and free from vacuolation but may be fibrillar and somewhat vacuolated under shorter exposures. Clefts are frequently seen. The nuclei are irregular in shape and staining and occasionally are vacuolated. The interfibrillar spaces are wide and contain a little albuminous material. In *duodenum* the contractile material is usually hyaline or translucent and swollen, vacuolation is common with prolonged exposures. The nuclei are very irregular in shape and staining; vacuolation is not very common; occasionally 'ghosts' are seen. The interspaces are often wide and oedematous. In *jejunum* the appearances resemble those in duodenum but are a little less marked. In *ileum* the contractile material is hyaline and swollen, sometimes translucent, rarely fibrillar, slight vacuolation is rather common. The nuclei are faintly stained as a rule and are often vacuolated.

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In *colon* the contractile material is hyaline, sometimes fibrillar, and may be swollen but rarely is translucent, vacuoles and clefts are seen with moderate frequency. The nuclei vary in shape and staining but may be vesicular or vacuolated and may split longitudinally. In *rectum* the contractile material is hyaline, frequently swollen or cloudy or translucent. Vacuoles and clefts are common. The nuclei are faintly or deeply stained and rarely show vacuolation. In *large artery* the contractile material is hyaline, sometimes translucent or granular, rarely fibrillar and sometimes vacuolated. The nuclei are irregular in shape, faintly stained, sometimes swollen or vacuolated. In *arterioles* the contractile material is homogeneous but vacuolation of nuclei is frequently seen. *Fallopian tube* in the two females of the series presented widely different appearances. In the parturient animal (QC, 64 hours) the contractile tissue was fibrillar, translucent and showed clefts, while the nuclei were irregular, contracted and deeply stained. In the other animal (QA, 96 hours) the contractile material was hyaline, clefts were numerous though vacuoles were few and the nuclei were faintly stained, often vacuolated and sometimes were empty sacs.

Cardiac Muscle.

The contractile material is usually hyaline but may be slightly granular or fibrillar, striation is apparently wanting under shorter exposures but traces may be found under longer exposures. Fragmentation of the fibres is common, and under shorter exposures there may be vacuolation or occasionally translucency. The nuclei are short thick rods varying somewhat in appearance but usually faintly stained, 3–4 times as long as broad (normal cat $4\frac{1}{2}:1$) and showing little particulate chromatin. Nuclear vacuolation occurs in many cases and vesicular forms or ' ghosts ' may be found. The intermuscular spaces are wide and contain a small amount of amorphous granular material but no adventitious cells.

Connective Tissue.

In the dense variety the tissue is often swollen and collagenous, and fibrillar structure is not marked but sometimes the fibrils are cloudy and granular. In the loose variety the fibrils are usually swollen and granular but they may be gelatinous or mucoid in appearance. The only nuclei present are a few contracted and deeply stained connective tissue nuclei and pale endothelial nuclei.

Endothelium.

Over the *stomach*, with shorter exposures, the endothelium is a little shreddy or becoming detached, with longer exposures, it is entirely disintegrated. The nuclei, in the former case, are apt to be swollen or vesicular, in the latter, are deeply stained or have disappeared entirely. Over *duodenum* the appearances vary much but usually the layer. is shreddy and the nuclei stain deeply. Over *jejunum* the appearances are similar but strips of detached

endothelium may be found in which there is no evidence of nuclei. Over *ileum* the endothelium is moderate or fair in a few instances but is usually much degenerated and desquamated. Over *colon* and *rectum* the endothelium is moderate but often partially detached and the nuclei stain intensely. The condition of endothelium over the large intestine is uniformly better than that over the small intestine in the same animal, but the general degree to which the endothelium is affected varies within fairly wide limits. Over *spleen* the endothelium is better preserved than over stomach or intestine but is often broken and partially detached; the nuclei are occasionally swollen or vesicular and stain faintly but, as a rule, are irregular in shape and stain intensely. Within the substance of the organ endothelial cells show a conglomerate cytoplasm : the nuclei are large and irregular in shape, sometimes stain faintly but often stain deeply if the exposures have been 48 hours or longer. In *lymphatic glands* they are often large and crammed with débris of red blood corpuscles; similar cells are not found in the spleen. In *lung* endothelium attached to the alveolar walls shows irregular, deeply and diffusely stained nuclei and pale, homogeneous, conglomerate cytoplasm. Few cells are desquamated and these may contain a little black pigment. In *large arteries* the endothelial layer is usually attached, and the nuclei are linear and deeply stained, but in *veins* and (even in arteries with very long exposures) detachment and disintegration of the layer occurs and the nuclei may stain very poorly. In *arterioles* the endothelium is well preserved, the nuclei are somewhat irregular in shape and project into the lumen owing to contraction of the muscular coats and usually stain deeply and diffusely. Under a 96 hours' exposure desquamation of endothelium in even the arterioles may occur.

Liver.

The cohesion of the liver is poor, and in many cases the cells are separated from one another. The capillaries are wide and contain broken down red blood corpuscles or granular débris. The outlines of the hepatic cells are usually not well marked, the cytoplasm is hyaline or perhaps somewhat granular and may show lacunae the former seat of fat globules. The well-formed nuclei are round, show a little particulate chromatin and a nucleolus, but 'ghosts' and later stages of nuclear degeneration are numerous. In some cases the liver substance is definitely invaded by large bacilli and degeneration is extreme. The bile ducts share in the disintegration, their lining columnar epithelium is often partially detached, mucoid or otherwise degenerated and the nuclei are irregular in shape, vesicular and faintly stained or deeply stained and contracted. The lumen of the ducts may contain granular amorphous material. In some places proliferation of the lining epithelium of the bile ducts is suggested. In frozen sections stained with Sudan, Nile blue or osmic acid there is little evidence of lipoid. A very few large or a few small globules may be present but, though it is rare for sections to prove entirely negative, fat is an inconspicuous feature. The

liver of a normal cat contained large quantities of large globules staining pink with Sudan and pale lilac with Nile blue.

Spleen.

The organ is permeated to a varying but always considerable degree by broad, unstriped muscular and connective tissue trabeculae in the interstices of which the spleen pulp is found. This pulp is relatively acellular and the size of the spleen depends essentially upon the amount of stroma present. As a rule red blood corpuscles and non-haemal cells are in approximately equal amount. The red blood corpuscles are irregular in shape and stain poorly but are not broken down, and endothelial cells containing blood pigment or débris are almost wanting. Of the non-haemal cells the majority are endothelial but a few doubtful lymphocytes are also present. Malpighian corpuscles are not well-defined, and the nuclei of the cells present are large, pale and perhaps vesicular. In some cases they are little more than suggested by a concentric arrangement of the cells. Nuclear débris is practically absent.

Pancreas.

The coarse structure is well preserved, congestion may be present but no haemorrhages are seen. The acini are ill-defined, oxyphil centrally and peripherally as a rule, but occasionally the periphery of the acinus is basophil. The cytoplasm of the pancreatic cells is conglomerate and hyaline. The nuclei are large, round, faintly stained, nucleolated, often vesicular. Islands of Langerhans are usually numerous and distinct though they vary in size. They may present a few small sinuses. The cytoplasm is voluminous, conglomerate and finely granular, the nuclei are large, round or oval and staining varies but is usually faint and diffuse. The pancreatic ducts are surrounded by a large amount of collagenous connective tissue and are lined by a single layer of somewhat flattened cells with pale, vesicular nuclei. In most cases desquamation has occurred, perhaps accompanied by proliferation, and the lumen of the duct contains broken-down cellular and granular material.

Kidney.

The tissue is not congested though some of the larger blood-vessels contain blood ; no haemorrhages are present. The glomerular tufts may be a little shrunken, show patent capillaries with contained red blood corpuscles or, less commonly, are swollen and almost structureless. The nuclei of endothelial cells covering the tuft vary widely in shape, numbers and depth of staining. The endothelial lining to Bowman's capsule is usually poorly defined and may be partially desquamated while the capsule itself appears to be thickened. The glomerular space is usually empty but it may contain a few red blood corpuscles or a little granular albuminous material. The condition of the glomeruli appears to be worst in the case of longest exposures but the differences are not great. In the convoluted tubules paraffin

sections show a complete disorganization of the epithelium with obliteration of the lumen of the tubule. The renal cells are intensely vacuolated owing to removal of fat globules during preparation even in the least affected cases but, in those most affected, an irregular, granular material enclosing few and degenerate nuclei fills the lumen and is the sole representative of the renal epithelium. Hardly a normal nucleus persists but vacuolated forms, ' ghosts ' and constellations of chromatin points without nuclear membrane, or contracted masses of intensely stained material are numerous. In some of the most marked cases, even these evidences of nuclei fail and tracts of granular material are found without trace of nuclei. In the conducting tubules the epithelium is less affected, but desquamation may have occurred and often the lumina of some of the tubules (particularly in the pyramid) are obstructed by granular or epithelial casts. The cytoplasm of the cells in this region is scanty and hyaline or swollen, granular and breaking down. The nuclei vary in shape and staining but many are vesicular or ghost-like. As more unusual conditions there may be in the papilla intense congestion of capillaries or a cystic condition or complete disappearance of the epithelium in some of the tubules. The stroma is scanty, but the fibrils are often swollen and gelatinous or granular in appearance. The nuclei are few and stain deeply as a rule.

Frozen sections stained with Sudan show an intense collection of singly refracting fat globules confined to the convoluted tubules with great exactness. The conducting tubules may take the stain to a slight extent but there are no globules, and the glomerular tufts are practically unstained. The globules vary much in size even in the same convoluted tubule, and the entire renal epithelium in this region appears to have undergone the change. The phenomenon was observed in each of the cats that died and practically to the same extent in each. In a normal cat there is evidence of some lipoid formation in the cells of the convoluted tubules, and in an occasional tubule it may be intense, but the intense condition in the radiated animals is universal. With Nile blue the globules are pale lilac in colour as a rule, and stained globules do not appear to be so numerous. The same is true with osmic acid under which black globules are relatively few, but (smaller) grey green globules are numerous.

Adrenal.

The zona glomerulosa is narrow, the cells usually are somewhat small and shrunken, the cytoplasm hyaline or granular and possibly showing some small lacunae, the former sites of fat globules. The nuclei vary in shape and staining, in some cases being round, well defined, faintly stained, provided with particulate chromatin, in others being small, deeply and diffusely stained. A few ' ghosts ' are found in the zona glomerulosa. In the cortex the cells are large as a rule and polygonal, the cytoplasm is finely foam-like or may be granular, some lacunae are present the former seat of fat globules. The nuclei are large, round, pale and nucleolated ; ' ghosts ' and even more degenerated forms are

numerous. In the case of longer exposures the nuclei appear to be smaller and stain moderately deeply, and diffusely. In the medulla there is a suggestion of alveolar arrangement and large blood-containing or empty sinuses are found. The cytoplasm is conglomerate and is represented by finely granular material. The nuclei are round, often poorly defined and vary much in depth of staining; in some cases ' ghosts ' are numerous.

In Cat QF (exposure of 90 hours) the adrenal showed foci of calcification and, in Cats QC (30 hours) and QE (95 hours) bacilli were present in the blood-vessels.

Frozen sections stained for lipoid were made in four cases. With Sudan lipoid was always present in the cortex, but its distribution was patchy or possibly confined to a special part. Thus in one case, it was only seen in an outer ring next the zona glomerulosa and an inner ring next the medulla. In another case the lipoid was confined to the middle third of the cortex. With Nile blue, pink or even lilac, globules were few, but the cortex showed regions in which were numbers of deep blue or purple globules. In one case (QE, 95 hours) no pink globules were present, but a fine blue granular deposit was found. With osmic acid few of the globules—chiefly those of larger size— stained black, the majority were of a greyish green colour. There is in all cases a considerable diminution in the amount of doubly refracting fat.

Stomach and Intestines.

Towards the cardiac end where the epithelium was squamous, it was thin and much desquamation had occurred, the cytoplasm of the cells was structureless, and the nuclei were large and vesicular. The mucosa towards the cardiac end and towards the pyloric end, though there was some difference in arrangement, presented similar changes. In the majority of cases the investing epithelium was altered profoundly. Sometimes it had completely disappeared, sometimes traces alone were present, sometimes it was the seat of extensive mucoid degeneration. In the tubular glands a similar range of changes was found. At the one extreme were some instances in which practically the entire secreting system of the stomach had disappeared and the mucosa was represented by little more than a swollen haemorrhagic or oedematous stroma in which the fibrils had undergone gelatinous or collagenous degeneration. At the other extreme, viz. the least affected cases, there was great mucoid degeneration of the secreting epithelial cells, and the nuclei were large and vesicular, but the tubules were moderately well preserved. Here the great majority of the cells show an oxyphil, structureless cytoplasm, but towards the blind ends of the tubules are a few isolated, ill-defined cells of which the cytoplasm is scanty, finely granular and basophil. The more intense destruction was found where survival was longer. In animals that died under, or shortly after, exposure the changes were less, even though the exposure lasted for 90 or more hours.

In *duodenum* the investing epithelium has almost entirely

disappeared and the connective tissue of the villi is laid bare. The tubules are short, wide, and filled with a desquamating epithelium which has undergone much mucoid degeneration or the greater part of the epithelium has disappeared altogether. Where the epithelium persists, the cells are swollen, the cytoplasm clear, the nuclei are faintly stained and vesicular. Goblet cells are numerous, and the lumina of the tubules and of the gut contain much mucus along with desquamated epithelium. Occasionally a few chromatin masses suggestive of mitosis are seen. The fibrils of the oedematous stroma are gelatinous or collagenous and sometimes superficial necrosis occurs. The nuclei present may be swollen and ruptured, but the majority are contracted and stain deeply. Brunner's glands are poorly represented. In *jejunum* the changes are similar but somewhat less marked, in particular the evidences of investing columnar epithelium are greater though mucoid degeneration and goblet cell-formation therein are pronounced. In *ileum* the investing epithelium has disappeared to a large extent and there is some superficial necrosis of the denuded stroma. The tubules are short and wide, and goblet cell-formation is pronounced. They may be converted into bags of mucus or, the mucus having been discharged, the epithelium of the tubules is represented by empty and more or less desquamated goblet cells. Where nuclei are seen they are round, swollen or vesicular, poorly defined, and may stain faintly or intensely. Forms suggestive of mitosis are occasionally found. The stroma is oedematous, may be scanty or voluminous, the fibrils are collagenous and the number of cells present varies considerably. Usually the nuclei are those of endothelial, small mononuclear, unstriped muscle and connective tissue cells; staining is deep and nuclear shape is irregular. The lumen of the gut contains much mucus and cellular débris.

In *colon* there is no investing epithelium, the tubules are represented by rows of full or empty goblet cells or are converted into mere bags of mucus. Such nuclei as persist are usually contracted, deeply stained and thrust close against the basement membrane, but may be pale and ill-defined. The stroma is scanty, the fibrils collagenous, the nuclei few, contracted and deeply stained, or faintly stained and showing a nucleolus. In *rectum* the appearances resemble those of colon but may be either more or less intense.

Generative System.

Testicle. In the testicle the contents of the seminal tubules are usually somewhat contracted and the cells vary in numbers and arrangement. Cells of Sertoli may be few or fairly numerous; the cytoplasm and the large oval nuclei are pale and ill-defined. Spermatogonia and spermatoblasts are rarely seen, but spermatocytes, in more or less disorderly arrangement and in two or three layers, lie peripherally in the tubules. The spermatocytes show little cytoplasm, but have large round nuclei which may be faintly or moderately and diffusely stained, or deeply stained and showing evidence of irregular mitosis. When spermatogonia are present

they also may be either in prophase or in the resting stage. Numerous intensely basophil spermatids are present in most cases and may be arranged fanwise. Some of the spermatids are neutral in staining but definitely oxyphil forms are not seen. Spermatozoa are unusual and when present are ill-formed and stain indifferently. The intertubal tissue resembles that of cortex of adrenal in the presence of large polygonal cells with foam-like cytoplasm and round, pale, nucleolated nuclei. It is present in small but definite amount, and is slightly vascular. The epididymis is not very well preserved, though better than the testicle itself. It shows a series of tubules lined by a single layer of columnar epithelium. The cytoplasm carries long cilia, is voluminous, finely granular, less dense beneath the homogeneous layer which bears the cilia, and the nuclei are oval, pale and nucleolated. The lumina of the tubules are usually empty except for a little débris, but spermatids, spermatozoal heads or spermatozoa may be present in small numbers. In only one of the five males examined (QF, 90 hours) were spermatozoa numerous.

Ovary. Only two cases were available for examination, one of which was parturient. Both ovaries contained large corpora lutea in varying stages of development. A well-marked layer of ovules and Graafian follicles was present, but the ovules were large and degenerated, sometimes contracted away from the surrounding tissue. They contained large, oval, faintly staining nuclei set in hyaline, finely granular cytoplasm, but not infrequently no nucleus was seen. There was no evidence of vacuolation. The stroma was loose and oedematous in one case, the seat of haemorrhage in the other.

Lungs.

The organs were usually the seat of considerable congestion and sometimes haemorrhage or oedema or consolidation was superadded. The alveolar walls showed many dilated capillaries which might be full of blood or empty. The alveolar spaces, when consolidation existed, contained coagulated, homogeneous, albuminous material and presented appearances resembling those of lobar pneumonia except that the consolidation was patchy, that polynuclear leucocytes were absent, and that compensatory emphysema was also present. Very little desquamation of endothelium had occurred. The bronchi showed numerous goblet cells and great mucoid change of their lining columnar epithelium, and some foci of consolidation were arranged round a completely blocked bronchiole. Cilia were not often visible and were short. In some cases considerable proliferation of epithelium associated with desquamation was present rather than the formation of mucus.

Thyroid.

The acini varied considerably in size and in the majority of cases were completely filled with colloid; partially filled, half empty, and even a few empty acini were found in Cat QA (96

hours). The epithelium lining the acini was regular, homogeneous, presented little cytoplasm, was not vacuolated and the nuclei were small, round, faintly and diffusely stained, and no 'ghosts' nor nuclear débris were visible. Many large bloodvessels were present containing red blood corpuscles but no leucocytes; extravasation was doubtful. Preservation of the tissue appeared to be remarkably good.

Parathyroid.

A regular mass of sharply defined, closely packed cells without evidence of alveolation. The cytoplasm was conglomerate and scanty, and the nuclei were round or oval, faintly or moderately and diffusely stained, though they might show a nucleolus or a little particulate chromatin. A small amount of delicate connective tissue with intensely stained nuclei permeated the mass of cells.

Lymphatic Gland.

Although a great deficiency of non-haemal cells was a constant characteristic, glands taken from different regions in the same animal differed somewhat in appearance, according as the number of cells was less or the amount of blood present was greater. In almost all cases blood was present to a considerable degree, but sometimes actual haemorrhage appeared to have occurred. The non-haemal cells found were chiefly endothelial or plasma cells, but small mononuclear cells were also present in small numbers, together with a few lymphocytes. Germinal areas composed of endothelial cells were ill-defined. In the lymph sinuses of the gland (peripheral and central) few cells were present other than red blood corpuscles and large isolated endothelial cells. The latter might be crammed with corpuscular débris to such an extent that the nucleus was barely visible or might present oval or irregular, deeply stained nuclei and vacuolated cytoplasm. Though many nuclei were seen to be undergoing degeneration nuclear débris was practically absent. In some of the glands irregular foci of non-corpuscular albuminous coagulum were seen.

Salivary Gland.

The tissue was well preserved, and presented numerous acini, of which the cytoplasm was finely granular and basophil. Intermingled with these were smaller numbers of larger acini, of which the cytoplasm was oxyphil and relatively free from granules. The nuclei of both types of acinus were small, round or oval. Minute canaliculi were seen in the centres of the acini. The ducts were numerous, lined by a low columnar epithelium with scanty, oxyphil, non-granular cytoplasm. In the case of many of the ducts an amorphous, coagulated material fills the lumen.

Bone-Marrow.

(Cat Q 1, 48 hours, alone examined.)
The tissue was highly congested and showed many haemo-

rrhages, few cells were present, and these were in various stages of degeneration. No cells definitely bore granules. A few multi-nucleated giant cells were seen.

SUMMARY OF RESULTS

Changes Observed during Life of the Animal

During actual irradiation nothing abnormal is observed unless the exposure be very prolonged when phenomena are met with similar to those that occur in animals surviving some days after shorter exposures. The most pronounced phenomena are: (1) changes in the circulating blood; (2) increased formation of mucus; (3) diarrhoea; (4) somnolence.

The blood changes concern erythrocytes and leucocytes, and are essentially destructive. They have been considered in some detail for rabbits (p. 84) and cats (p. 98). Of all the changes in the circulating blood, destruction of lymphocytes is the most characteristic. It obtains in all the species of mammals examined, even when the exposure to gamma radiation is short. Its counter-part is met with in the histological changes of spleen and lymphatic glands. Polynuclear cells resist destruction for a long time, but ultimately they are destroyed if the exposure be pro-longed. Large and small mononuclear cells resist destruction to a far greater extent than lymphocytes. Under the conditions of experiment no increase in numbers of lymphocytes was ever seen, but the numbers of polynuclear cells and erythrocytes increase as the result of short irradiation, though ultimately a general anaemia and leucopenia results if the exposure be prolonged. Haemorrhage, as a symptom during life, occurs, but only with excessive ex-posures. The changes in circulating blood can be correlated with changes in the bone-marrow. If the exposure be not too severe, there are signs of recovery in the rabbit about the tenth day of survival.

Increased formation of mucus and diarrhoea may be taken together, for the diarrhoea depends in some part upon excessive formation of mucus, as is seen histologically. In rabbits, increased mucus formation is little evident, but in cats it is pronounced, particularly in the mouth and upper respiratory tract, and in colon and rectum. Swelling of salivary glands is sometimes noted and should probably be associated with that plugging of ducts by mucus that is found histologically.

Somnolence is most marked in cats, but a disinclination to move is noted in all animals in which exposure is prolonged. There was no indication of pain throughout the entire series of experiments. In one cat convulsions occurred shortly before death, but there was no evidence that they were associated with pain.

In one cat abortion occurred. Another cat, though subjected to a considerable exposure, survived, and since exposure has borne

two litters of kittens. Loss of weight was noted in rabbits and, if the exposure were not too severe, it was only temporary. In one cat exposed for 6 hours at 4 cm. epilation commenced on the 18th day, there was superficial excoriation on the 25th day, a large area of baldness 5 weeks after exposure, complete healing, and fine downy hair 3 months after exposure.

<div align="center">LETHAL EFFECTS.</div>

It is possible to kill an animal by irradiation alone, but it is necessary to recognize primary and secondary effects, though the two are not always easy to separate. The death itself seems to be due chiefly to secondary effects, for, though a rat dies under about 45 hours' continuous exposure to 5 gm. of $RaBr_2$, at a distance of about 4 cm., death also occurs with fair regularity within two days after an exposure lasting 6 to 12 hours. Six hours appears to be about the minimal lethal exposure for the rat under these conditions. Whether the animal have died under continuous irradiation or have died some 42 hours after an exposure of 6 hours the changes met with in the tissues are very similar. Nevertheless with prolonged irradiation the changes are more intense.

In comparing the minimal lethal dose in different animals the size of the animal is a factor. The radium is contained in a flat circular brass box, 14 cm. in diameter, and the intensity per unit of surface is fairly evenly distributed. But it is obvious that a frog, a rat, a rabbit, and a cat exposed 'as close as possible' will receive very different total amounts of irradiation of specific organs. The fall in intensity of the radiation owing to distance has been determined experimentally by Professor Russ (p. 8) and, in the animal experiments, the distance has been taken as that which obtained between the surface of the radium box and the mid-point of the animal in a crouching position. Owing to the different arrangements adopted, the mid-point of the frogs and of the rats was distant from the $RaBr_2$ about 4 cm., the mid-point of the rabbits and the cats was distant about 15 cm. And since, at 4 cm. and 15 cm., the intensity of irradiation has fallen to about 65 per cent. and 13 per cent. respectively, it follows that an exposure of one hour at 4 cm. is equivalent to an exposure of 5 hours at 15 cm.

When these corrections have been made an extraordinary difference is observed between the cold and the warm blooded animals, for the frog will support some 12 to 20 times as much gamma-radiation as the rat, rabbit or cat. As to the latter animals it is not safe to dogmatize. The minimal lethal dose for the rat at 4 cm. is about 6 hours, while for the cat, at 15 cm., it is about 24 hours, and for the rabbit, also at 15 cm., it is about 48 hours. These values, corrected for the fall in intensity at the two distances, indicate that under similar conditions when the minimal lethal exposure for the rat is 6 hours, for the rabbit it is 9 to 10 hours, and for the cat it is 5 hours. Hence it may be assumed provisionally that these three types of animals are not

equally susceptible to gamma-radiation. The cat, in particular, gives the impression of being highly susceptible.

Post-mortem Appearances

Under shorter exposures, even though death may have occurred after some days of survival, naked eye changes are practically confined to distension of the stomach and intestines by liquid contents mixed with gas. The lungs may be mottled or partially consolidated, or show foci of inspissated mucus, or regions of collapse interspersed with compensatory emphysema. The organs in general are moderately full of blood and soft, but no haemorrhages are present.

Under greatly prolonged exposures haemorrhages occur (particularly in cat and rabbit) in various tissues and may be very extensive into muscles, the lining membrane of cavities (stomach, bladder), lymphatic glands, sex-glands, and bone-marrow. In such cases, subserous petechial haemorrhages also occur and, inasmuch as bacteria are sometimes found in the tissues, the haemorrhages may be in part septicaemic. In these cases also the distension of stomach and intestine is very great, and the coats are translucent and torn with ease, while large amounts of mucus are obvious with or without admixture of altered blood.

In all the species of animals used in the investigation, the small size of the spleen after exposure to gamma rays is noticeable. Since the spleen is roughly triangular in cross-section, my estimate of its cubic content is half the product of its length, breadth, and height, and I divide the value thus obtained by the length of the extended animal from tip of nose to root of tail. Below are given some mean values obtained in rats, and expressed in the form of cubic centimetre of spleen per centimetre of length of animal :

Spleen of 9 control rats (non-radiated) = 0·072 c.c. per cm. of length.

Spleen of 12 rats exposed for 3 hours = 0·0358 c.c. per cm. of length.

Spleen of 10 rats exposed for 12 or more hours = 0·0182 c.c. per cm. of length.

The splenic condition is progressive, for, if the 12 rats exposed for 3 hours be divided into classes according to the length of their survival after irradiation, the values are as follows :

Killed immediately after exposure, spleen = 0·0521 c.c. per cm. of length.

Survived 3 days after exposure, spleen = 0·0322 c.c. per cm. of length.

Survived 6 days after exposure, spleen = 0·0287 c.c. per cm. of length.

Survived 9 days after exposure, spleen = 0·0157 c.c. per cm. of length.

Similarly in rabbits, whereas a normal spleen constituted 0·079 c.c. per cm. of length, the mean value in the entire series of irradiated animals was 0·014 per cm. of length with a maximum of 0·03 c.c. and minimum of 0·006 c.c. When the point is considered in a series of rabbits exposed for 16 hours, and allowed varying periods of survival, the following figures are obtained. They indicate a tendency to recovery after the initial diminution in size :

Control rabbit, spleen = 0·079 c.c. per cm. of length.
Rabbits killed immediately after exposure, spleen = 0·0125 c.c. per cm. of length.
Rabbits surviving 3 days after exposure, spleen = 0·0067 c.c. per cm. of length.
Rabbits surviving 6 days after exposure, spleen = 0·0092 c.c. per cm. of length.
Rabbits surviving 9 days after exposure, spleen = 0·0224 c.c. per cm. of length.
Rabbits surviving 16 days after exposure, spleen = 0·0135 c.c. per cm. of length.

In cats the phenomenon is not marked to the same extent, probably because of the great amount of stroma that enters into the composition of the spleen in these animals.

Among conditions that are somewhat more debatable, the following may be mentioned. Animals in which the exposure has been prolonged, frequently show either an abnormally dry or an abnormally moist condition of the skeletal muscles and subcutaneous tissue. In such animals, lymphatic glands and thyroid body may be extremely hard to find, partly because of general shrinkage, partly because of their incorporation in extravasated blood. In several instances numerous portions of tissue were selected for histological examination of these organs with negative results.

MICROSCOPICAL APPEARANCES

Cytological Appearances in General.

If the cell be considered in respect of its nucleus, its cytoplasm and any paraplastic material it may contain, marked changes may be found. The nucleus may stain faintly and diffusely (endothelium), deeply and diffusely (spermatogonia), faintly and with a few dust-like particles of chromatin (striated muscle), moderately and with a large nucleolus and a few particles of chromatin (liver), faintly and with a few relatively large particles of chromatin (kidney), and in many cases it is impossible to determine whether the appearances are normal. But in some cases it is certain that the nucleus is abnormal. It may be converted into an empty sac (columnar cells of intestine), or may be vacuolated (striated and unstriated muscle, bone-marrow), or may be ghost-like (liver, kidney, muscle), or the nuclear membrane may have disappeared, leaving only a small constellation of chromatin points (kidney, liver), or the entire nucleus

may have become broken up into deeply stained débris (lymphocytes, intestinal mucosa), or, finally, all traces of a nucleus may be lost, though cytoplasm persists (liver, kidney).

Even under normal conditions mitotic figures are rare except in intestinal mucosa and testicle. In the case of animals that have been killed immediately after a relatively short exposure, the cells of the tubular glands in the intestine may show irregular masses of deeply stained chromatin representing mitotic figures, but they are usually absent from testicle. If the animal have been subjected to a more prolonged exposure, or have been allowed to survive for some days, probably no trace of mitosis will be found even in intestinal mucosa.

The cytoplasm may be hyaline and basophil, oxyphil or indifferent (pancreas), translucent and oxyphil (gastric mucosa), vacuolated (bone-marrow, kidney, unstriated muscle), or it may be converted into mucus (intestine, trachea), or show fine granules (salivary gland), or globules of lipoid (adrenal, convoluted tubules of cat), or, rarely, it may show neutral fat globules (tracheal cartilage, paraortic tissue of rat, kidney of cat). Of these modifications the intense mucoid change in intestine and the lipoid change in kidney of cat will be referred to later. But perhaps the most striking change of cytoplasm seen after exposure to a large quantity of radium is its complete disappearance. In this case the nucleus is left suspended, as it were, in the middle of a cavity limited, at some distance, by the cell membrane which, now, is unusually conspicuous. Since the condition is most marked in animals that have survived for some days after a somewhat severe exposure, this disappearance of cytoplasm must be regarded as secondary. It has been found chiefly in cells of liver and in renal cells lining the conducting tubules.

Including zymogen granules and mitochondria under the general name of paraplastic material, little can be said with certainty. In salivary glands of serous type, fine basophil or oxyphil granules are present; in liver and pancreas somewhat coarse granules are often closely packed in cells; in peptic cells of stomach there is a fine basophil granulation, and in the oxyntic cells a small amount of fine oxyphil granulation. But these appearances cannot be distinguished from the normal. With regard to mitochondria, the uncertain nature of the objects designated by this name renders observations in regard to them of doubtful value, particularly if negative. I have found them in liver and kidney and, doubtfully, in specimens of intestine in rats that have been exposed for 16 hours, but I am not convinced that they are present in other varieties of cells examined.

Blood in Blood-vessels and Tissues.

Sometimes the red corpuscles are discrete, sometimes converted into conglomerate and homogeneous masses. As a rule staining is only fair, but the corpuscles may stain well. In frogs the nucleus of erythrocytes stains very faintly when the exposure is prolonged. In frogs and, to a certain extent, in rabbits and

cats under conditions of prolonged exposure, non-corpuscular coagulum is met with in some of the blood-vessels and may be found as masses in the tissues. Thus part of the whole glomerular tuft may be converted into a lardaceous-like material, irregular masses may be found in the spleen, or albuminous material may be found in the glomerular space. In the liver the capillaries often contain little more than débris of erythrocytes and, in severe cases, pigment-bearing endothelial cells are found in the spleen, while the sinuses of the lymphatic glands contain many macrophages in which the large amount of yellow corpuscular débris obscures the nucleus entirely. The very few leucocytes present are almost always polynuclear unless the animal be recovering after exposure when some lymphocytes may be found. The different behaviour of lymphocytes and polynuclear cells under gamma radiation is shown by the blood within capillaries of lymphatic glands.

Striated Muscle.

Appearances found in all the species of animals used for experiment are (1) progressive loss of striation with increasing length of exposure or survival after a severe exposure ; (2) a patchy translucency, less marked with prolonged exposures, that affects portions of fibres and groups of fibres, and is associated with irregular deposition of amorphous, oxyphil, albuminous material over the fibres; (3) dilatation of the intermuscular spaces with local depositions of granular material, but no adventitious cells ; (4) irregularity in degree of fibrillation with cloudy or granular changes in some of the fibres ; (5) nuclear changes; (6) lipoid deposit.

The nuclei vary little in staining when they are viewed on the flat; 'ghosts' are rare, but vacuolated forms are seen when exposure has been prolonged, and particularly when this has been associated with survival. The shape of the nuclei as determined by rough measurements of the ratio length : breadth differs under different periods of exposure and survival. In the frog (gastro-cnemius) there is a progressive swelling of the nucleus so that the ratio length : breadth which in the normal animal is $9:1$, becomes $4\frac{1}{2}:1$ when exposure is prolonged. Similarly, in rabbits (abdominal muscle) exposed for 16 hours the ratio length : breadth which in the normal animal is $6\frac{1}{2}:1$, becomes about $6:1$ after 3 days' survival, and $3\frac{1}{2}:1$ after 6 and 9 days' survival. Though survival is associated with nuclear swelling the opposite condition of nuclear contraction appears to be a very early change after moderate exposure, and may be the result of prolonged exposure in rats, rabbits, and cats. Thus the ratio length : breadth of nuclei in abdominal muscle of a normal cat is about $3\frac{1}{3}:1$, but in cats exposed for prolonged periods the ratio is $8:1$ or more. Further, though survival is associated with swelling of the nuclei in striated muscle, if recovery take place the return to normal is interrupted by a late, short period of nuclear contraction.

The lipoid change is not seen in every case, though found in each species of animal used. It is a phenomenon of survival and

appears to require exposures of medium length since it is absent when the exposure has been either very short or greatly prolonged. It is associated with undue staining of the muscle fibre by the lipoid dye. Normal muscle fibres take Sudan or scarlet very little even when steeped therein overnight. Hence under short radium exposures there is neither lipoid deposit nor staining of fibres ; under medium exposure and survival, portions of fibres take the stain moderately and diffusely, and dust-like, intensely stained lipoid globules are present in these portions ; under prolonged exposure to radium fair numbers of fibres may stain diffusely but discrete lipoid globules are absent.

Muscles in the same animal do not necessarily react to the same extent. It is generally true that in any given animal exposed to gamma radiation the biceps cubiti is less affected than the muscles of the anterior abdominal wall.

Unstriated muscle.

A swollen, hyaline, rarely fibrillar condition of the contractile material is characteristic of this tissue in all the species of animals, and vacuolation is common. The degree of swelling varies according to the length of exposure and of survival. The same is true ·in the main of vacuolation, but the degree and principal sites of vacuolation differ in different species. In frog and rat the greatest vacuolation is seen in gastric muscle; in rabbit and cat this tissue is relatively free from vacuolation though clefts are common ; more vacuolation is found in muscle of upper intestine. Contractile material of artery is hyaline, rarely fibrillated and frequently shows clefts or vacuoles.

The nuclei are long, tortuous or irregular, swollen, often vesicular or vacuolated, only occasionally ghost-like. Usually they stain faintly and show irregular disposition of chromatin but no discrete particles. They stain deeply and are linear when viewed in profile. Unstriated muscle of stomach and duodenum is the seat of the most marked changes, and when exposure or survival has been prolonged the fibres may be broken into small fragments and the nuclei lie in lacunae.

The intermuscular spaces in the frog after prolonged exposures are wide, and contain a mucoid or gelatinous material ; in the other animals, though the muscle is clearly oedematous, the intermuscular spaces are rarely very wide, and contain only a little granular non-cellular material.

The reaction (acid, indifferent, alkaline) of the muscle differs in different parts of the alimentary tract. Unstriated muscle of Fallopian tube appears to be less altered than that of other situations.

Cardiac muscle.

Making allowance for the different conditions of exposure, the appearances of heart muscle are closely similar in all the species of animal used for experiments. Striation persists after short exposures but is soon lost as exposure lengthens. The contractile material is finely granular and fibrillated with short exposures.

but becomes hyaline or translucent, vacuolated and fragmented as the exposure and the survival after exposure lengthen.

The nuclei, under short exposures, show finely particulate chromatin on a relatively unstained basis and therefore differ little from the normal in staining. On the other hand, rough measurements of the ratio length : breadth show swelling, and with long exposures this swelling is considerable.

In rabbit whereas the normal ratio is about $5\frac{1}{3}$: 1 it becomes about $3\frac{1}{2}$: 1 or even less after irradiation and survival. Again, in a normal cat the ratio was about $4\frac{1}{2}$: 1, and in those exposed to gamma rays it was about $3\frac{1}{2}$: 1. A similar but less pronounced change was seen in the frog. In rats exposed for 3 hours and surviving a certain amount of contraction was observed, the ratio being 5 : 1 in normal animals, and being in animals killed immediately after 3 hours' exposure 5.3 : 1, surviving 3 days, 5.5 : 1, surviving 6 days 5.6 : 1, surviving 9 days 5.3 : 1. Similar but more severe contraction was seen in two rats exposed for 48 hours, the ratio being 6.5 : 1 and 6.8 : 1.

Nuclear vacuolation or vesiculation becomes common as radiation and survival are prolonged. 'Ghosts' may be found under the most severe conditions of irradiation or survival but are not common.

The intermuscular spaces are usually wide, but contain no adventitious material or cells in the majority of cases. Under conditions of moderate severity they may contain a little amorphous, granular material, and under the most severe conditions extravasated red blood corpuscles may be found. In no case has lipoid deposit been found in the fibres.

Connective tissue.

In the mammals examined, the fibrils of dense connective tissue become collagenous and fibrillar arrangement is obscured. Loose connective tissue fibrils are usually fairly granular but may be swollen, gelatinous or mucoid. In the frog the gelatinous character is marked, the fibrils are swollen, very rarely granular, and the interspaces are filled with a watery or mucoid material. In all animals cells are few, and the nuclei are more or less deeply stained (connective tissue) or faintly stained (endothelial). There is no evidence of cell proliferation, and no adventitious cells are present. The changes indicated are little marked with shorter exposures.

Endothelium.

The condition of endothelium varies widely even within the same animal. The best specimens of endothelium are met with in arterioles. Next below these come arteries and veins, the investing endothelium of spleen, sex glands and pulmonary alveoli. In these regions endothelium is often good. The worst specimens occur over the gastro-intestinal tract, but even here there are differences for the endothelial covering of colon and rectum is better than that of stomach or small intestine. The worst endothelium of all is found over duodenum, but that over jejunum

is little better. Over stomach and ileum the condition of endo-
thelium is also bad. In the regions where endothelium is good
a regular layer is present, and the cells viewed on the flat show
round and faintly and diffusely stained nuclei in a relatively
large amount of unstained cytoplasm, viewed in profile the cells
may be linear and deeply stained or swollen or occasionally
vesicular. At the opposite extreme, traces alone of endothelium
may be found, and in these such remnants of nuclei as persist may
stain so faintly as to be barely recognizable or may stain intensely.
Such widespread detachment and disintegration of endothelium
covering the gastro-intestinal tract follows prolonged exposures
or survival after moderate exposures in all the varieties of
animals examined. When exposure has been extreme detach-
ment of endothelium may be noted even in arteries of smaller
calibre. Within the substance of tissues endothelial cells appear
to be far less vulnerable. In spleen, lymphatic glands and lung,
the cytoplasm of endothelial cells is conglomerate and the nuclei
often pale and somewhat irregular and large. Isolated endo-
thelial cells, whose nuclei are obscured by débris of red blood
corpuscles or, in the lung, by a few carbon particles, may be pre-
sent. The experiments afford no evidence that gamma radiation
is associated with proliferation of endothelium.

Liver.

There is a general congestion with diminution in cohesion of
the tissue which increases as exposures are lengthened. The
widely dilated capillaries contain partially broken down cor-
puscles or mere corpuscular débris, but, in the frog under pro-
longed exposures, they may contain non-corpuscular thrombus.
In frog and rat and cat focal necroses may be found, and, in the
cat, these may be the seat of definite bacillary growth. The
hepatic cells are polygonal in outline, and the degree to which
the outline is visible varies much. Apparently it comes into
view as the cytoplasm becomes finely and then coarsely granular,
and subsequently disappears, changes which are observed as the
result of prolonged exposure and especially of survival after
moderate or severe exposures. The nuclei are round, even in
size, faintly stained, often nucleolated and show a little particulate
chromatin, but 'ghosts' are very numerous, and more degenerate
nuclear forms are common. In the more severely affected cases
nuclei may disappear altogether and groups of liver-cells then
consist of cytoplasm alone. When the cytoplasm of the hepatic
cells has disappeared to a considerable extent the nucleus often
becomes swollen, irregular in outline, and stains deeply and
diffusely, and lies more or less naked within the cell at a distance
from the now unusually distinct cell membrane. The appearance
is most often seen in frog but also occurs in rat and rabbit. In
some cases (especially rabbit) paired nuclei of equal size but
somewhat smaller than the normal are seen in great numbers.
Throughout the entire series of animals there is little evidence of
fat or lipoid in the liver, and siderosis has not been found. The
bile ducts are lined by a low columnar epithelium of which the

cytoplasm is homogeneous and the nuclei faintly stained or vesicular. The cells are often swollen, and the lumen may be occluded by a plug of thrombus. In frogs after prolonged exposures bile ducts may cease to be recognizable.

Spleen.

Reference has already been made to the diminution in size of the organ which follows on exposure to the gamma rays. This is associated with a deficiency of the essential cells of the spleen pulp, though a relative preponderance of red blood corpuscles is often recognizable. The lymphocytes disappear almost entirely with the result that Malpighian corpuscles are composed of little more than pale endothelial cells and lose their characteristic definition to a large extent. In animals killed immediately after a moderate or long exposure much intensely basophil nuclear débris is usually present in the Malpighian corpuscles, and to some extent in the spleen pulp generally. This nuclear débris disappears rapidly, and little or none may be found even after a severe exposure if the animal have survived a few days. As will be seen later similar nuclear débris is also found in lymphatic glands but does not disappear from them so soon as from spleen. .Red blood corpuscles are present in varying but usually considerable numbers, and there is some evidence of disintegration. The endothelial cells are relatively little changed ; their nuclei are irregular in shape, stain faintly, show little chromatin and may be vesicular, their cytoplasm is rarely discrete. Occasionally small numbers of large endothelial cells containing red or brown pigmented material are present. Such cells are uncommon immediately after a moderate exposure but become more numerous later. After extreme exposures they are found under both conditions. In the cat they are rare in the spleen though common in lymphatic gland. The organ in rat and rabbit often shows irregular accumulations of plasma cells or of small mononuclear cells. In these animals as well as in frogs the stroma becomes more evident as survival is prolonged owing to progressive destruction of cells. If the exposure be relatively short, signs of recovery may be noted after about the ninth day of survival. No evidence of siderosis has been found.

Pancreas.

The general structure is well preserved, though the tissue sometimes presents a boiled appearance. As a rule preservation is better in cases where the exposure has been moderately long. The acini generally show a conglomerate, hyaline cytoplasm which is oxyphilic centrally and basophilic in the nuclear region at the periphery. In the cat, rabbit and rat, with longer exposures, the cytoplasm may be oxyphilic throughout. The cytoplasmic structure differs little according to length of exposure, though in frogs with very short exposures it may be vacuolated, or in rabbit mucoid with extreme exposures ; granularity is practically absent. On the other hand, the nuclei are progressively more deeply and diffusely stained or vacuolated or vesicular and

faintly stained or ghost-like as exposure or survival after exposure lengthens. In the rabbit this obtains up to the ninth day after 16 hours' exposure, but subsequently the condition improves. Islands of Langerhans are found in the mammals examined, but are doubtfully present in the frog. They show no recognizable changes. The pancreatic ducts often lie in a voluminous sheath of swollen or collagenous connective tissue, and are lined by a layer of low columnar cells which may afford evidence of proliferation or desquamation. The nuclei are intensely vesicular and faintly stained. The ducts may be occluded by desquamated cells or mucus.

Kidney.

The organ is often congested and may be the seat of small haemorrhages when exposures have been prolonged. The glomeruli are profoundly affected in the frog. and in rabbit and cat under conditions of severe exposure similar, though far less pronounced, changes occur. Speaking generally, with shorter exposures, the glomerular tuft is somewhat contracted though numerous dilated capillaries are visible, the endothelium lining Bowman's capsule and covering the tuft is well preserved, and the glomerular space is practically empty. With survival after moderate exposures and after prolonged exposures the glomerular tuft swells and shows irregular foci of homogeneous, translucent or fibrinous material. the endothelium lining Bowman's capsule becomes degenerated and may be partially desquamated, and the nuclei of endothelial cells covering the tuft become vesicular. At the same time, amorphous, albuminous material with rare admixture of red blood corpuscles is found in the glomerular space. The number of glomeruli affected varies greatly. In the frog the condition is practically universal, in the cat it is fairly common under the conditions of these experiments, in rabbit and rat the glomerular change is slight though detectable.

In the convoluted tubules the appearances presented by frog, rat. and rabbit are very similar. They consist, under shorter exposures, in a swelling of the epithelium until the lumen is reduced to a mere cleft, and, under longer exposures or survival, in partial disintegration of the renal epithelium towards the lumen, and consequent widening of the lumen and bridging by strands of coagulated protein. Though the lumen may contain much degenerated cellular material, formed casts are rare. The remaining cytoplasm of the renal cells is hyaline, granular or vacuolated and basal radial striation is lost with all but the shortest exposures. The nuclei may be in fair condition, but in frog, rabbit, and cat 'ghosts' are numerous even where exposure to gamma radiation has been relatively short. When exposure has been prolonged or survival occurs after moderate or severe exposure, 'ghosts', constellations of chromatin points without nuclear membrane or non-nucleated tracts of degenerating cytoplasm, may predominate over relatively well preserved nuclei. In the frog the cytoplasm frequently disappears, leaving the nucleus, as it were. naked in the middle of the cell. In the

rat, nuclear changes appear to be less pronounced than in the other animals, and, in particular, ' ghosts' are not common. In the cat there occurs invariably an intense fatty change of the renal cells which is not present in any of the other animals used for these experiments. This change is sharply confined to the convoluted tubule system, and is absent from glomeruli and conducting tubules. Under Sudan staining of frozen sections the globules (singly refracting) are seen to vary in size, but are relatively large. In paraffin sections little cytoplasm is found, and the lumen of the convoluted tubules is filled with granular material or remnants of cells showing large vacuoles whence the fat has been removed during preparation. Such nuclei as remain are vesicular or faintly stained or mere 'ghosts'.

In the conducting tubules the changes of epithelium appear to be less pronounced. The lumina of the tubules are usually empty, but, towards the papilla, granular or hyaline or, more rarely, epithelial casts may be present, particularly if the exposure have been severe. The cytoplasm of the lining cells is scanty and translucent as a rule, but it may have disappeared, so that the nuclei are left naked in the cells, or it may have swollen, so that the lumen of the tubule is smaller than usual. The nuclei are sharply defined, faintly stained, often vesicular, and, with more severe exposures, 'ghost' forms are common. Under very prolonged exposures, changes in the conducting tubules are as intense as elsewhere, but even in the cat there is no evidence of lipoid formation.

The stroma of the kidney calls for no special remark except that, in the frog, it is occasionally the seat of accumulations of cells somewhat resembling plasma-cells in the possession of intensely oxyphil, non-granular cytoplasm. No other adventitious cells of any kind (except red blood corpuscles in extravasations) have been found in any other animals, and it is probable the cells occasionally present in the frog bear no relation to the exposure to gamma rays. The epithelium lining the pelvis of the kidney and extending into the ureter shows a tendency to disappearance of its cytoplasm and vesiculation or irregularity of its nuclei similar to that which occurs in the cells of the conducting tubules.

Adrenal.

The zona glomerulosa differs little in different animals and under varying exposures, but with prolonged exposures it may show a few small lacunae, the former seat of fat globules. In cortex the amount of lipoid (as represented by the lacunae) varies, being considerable in rat and little in rabbit and cat. It is chiefly confined to the outer half of the cortex, but the amount of lipoid appears to increase with exposure up to a point. On the other hand, when exposure is severe, few lacunae, due to its removal during preparation, are seen in the cells. The appearance of the cytoplasm varies considerably. When many lacunae are present the outlines of the large polygonal cortical cells are generally

well defined, the stroma finely granular and scanty, and the nuclei round, pale, vesicular, may lie almost naked in the midst of the cell. When lacunae are few and small the cytoplasm is finely foam-like or hyaline, and the outlines of the cells are little recognizable. Even under these conditions, however, the nuclei are often well defined, pale, nucleolated. Vesicular forms, 'ghosts', and even more degenerated forms of nucleus occur, but are not common. In the medulla there is usually a suggestion of alveolar arrangement, and large blood sinuses are present. The cytoplasm of the cells is conglomerate, finely and scantily granular, and interspersed in this material are round, usually faintly stained and vesicular nuclei. No differences have been detected in medulla according to length of exposure or survival. The medullary material is chromaffinic, and the cortex shows abundant lipoid in frozen sections stained with Sudan, but the distribution may be patchy or confined to special regions of the cortex. Both singly and doubly refracting globules of fat are present, but the amount of the latter is much less than normal. Occasionally the adrenal is definitely congested, but no haemorrhages have been found therein. In one cat foci of calcification were present.

Stomach.

The appearances of the muscular coats have been considered already.

The actual structure of the stomach varies in the different animals used, but the following composite picture is produced. Portions of the stomach, coated with squamous epithelium, present less marked changes than elsewhere. The Malpighian layer is irregular, and consists of a single row of cells of which the nuclei are vesicular and often lie in lacunae. Over this there is a definite layer containing eleidin granules, and varying numbers of keratinized layers undergoing desquamation. Few differences are noted under variation of exposure or survival. In the secreting portion of the organ in all animals concerned, the investing epithelium shows a progressive tendency to mucoid degeneration, disintegration, and desquamation, with vesiculation of its nuclei, as the exposure or survival after exposure is prolonged. In the tubular glands oxyphilic and basophilic cells occur, but the latter—usually confined to the blind end of the tubules—tend to disappear with severe exposures, and changes similar to those occurring in the investing epithelium are met with. In pronounced cases the secreting epithelium, as well as the investing epithelium, has disappeared almost entirely, and the gastric mucosa ultimately consists of a gelatinous, mucoid or oedematous, poorly cellular, stroma into which haemorrhage has taken place. Occasionally a few deeply-stained chromatinic masses are found which may represent mitoses. Goblet cells are absent or few, and, in slighter cases, little mucus is formed. Much mucus, however, is present where the exposure or survival after exposure has been prolonged.

Duodenum.

Here the condition varies in degree in the different species used, being most intense in the rat, but the essential features of degeneration, desquamation, and mucus formation obtain in frog, rat, rabbit, and cat. The changes show themselves after relatively short exposures and are rapidly intensified by more prolonged exposures or survival. With short exposures there is swelling and loosening of the investing epithelium and that lining the tubular glands. The cells show some desquamation and the nuclei become vesicular. No mitoses are seen, there are few goblet cells and little mucus is present. The stroma is rather scanty and contains few cells. As survival occurs after moderate exposures, degeneration and desquamation of the epithelium advance rapidly, much nuclear débris may be found in the blind ends of the tubules, goblet cells become numerous, and some ill-formed chromatinic masses suggestive of mitosis are found. The stroma becomes definitely oedematous and may contain many endothelial, small mononuclear, and plasma cells, but no polynuclear leucocytes are present. Owing to desquamation of the investing epithelium, superficial necrosis of the stroma sometimes takes place. Later, the condition becomes intensified when the lumen of the gut comes to contain much desquamated epithelium mixed with mucus, or, if the initial exposure has not been too severe, there is some improvement. The appearances found after increased length of exposure are similar to those just described, but under extreme exposures entire tracts of mucous membrane may undergo mucoid degeneration. Even the stroma—always less affected than the secreting elements—becomes intensely oedematous, while the constituent connective tissue-fibrils are gelatinous or collagenous. The Brunnerian glands ultimately undergo destruction, but their appearances differ from the normal less than the other elements of the mucosa. The mucosa of duodenum, like that of other parts of the intestine, rarely shows haemorrhages.

Jejunum.

The appearances in jejunum are similar to those in duodenum. They are usually more intense in rat and rabbit when the exposure has been prolonged, or at later dates of survival after a somewhat severe exposure. On the other hand, in the cat the investing epithelium of jejunum is better preserved although the seat of pronounced goblet-cell formation and mucoid degeneration. Nuclear and cellular débris may be present in quantity in the lumen of the gut and in the remnants of tubular glands, while there is always much mucus in the gut itself. In the rat the mucosa may be sloughing. Some deformed mitoses are found in the rat about the 6th day of survival after a small exposure.

Ileum.

The condition of ileum resembles that in the higher parts of the small intestine, but usually is rather less intense. Nevertheless,

pronounced changes are present, even to a complete sloughing of the mucosa in some cases. Goblet cells are numerous, and there is much desquamated epithelium and mucus in the lumen of the gut. Nuclear débris is found in the blind ends of the tubular glands, frequently the only portion that persists. The tubular glands may be converted into mere bags of mucus. Such nuclei as persist are vesicular or occasionally deeply stained and contracted. A few deformed mitotic figures may be seen. The stroma is voluminous as a rule, oedematous and moderately cellular, the cells being of the endothelial, small mononuclear, and occasionally plasma varieties. Some lymphocytes may be found, but polynuclear cells are wanting.

Colon and Rectum.

In the large intestine degeneration and desquamation are less marked than in the small intestine, but formation of mucus is the conspicuous phenomenon. Columnar cells seem to be converted into goblet cells to an extreme extent, both in the investing and the tubular epithelium. Most of the tubular glands show merely the outlines of cells, and deeply stained, contracted, or linear nuclei pressed against the basement membrane or partition between contiguous cells. The goblet cells may contain mucus, but in large numbers of cases they are empty and the mucus is found in the lumen of the gut. There is relatively little desquamation. Such columnar cells as have not become converted into goblet cells may show mucoid degeneration of their cytoplasm and a vesicular, faintly-stained nucleus. Mitotic figures are absent. In some instances isolated cells have undergone a peculiar degeneration and are converted into enlarged, oval, homogeneous masses that maintain the normal position of the cells concerned and are deeply stained. These oval, degenerated masses occur chiefly and are most numerous in the rectum, but are found in colon and occasionally in any part of the small intestine. The stroma is more extensive in rectum than in colon ; it may be oedematous with more severe exposures, and sometimes the connective tissue-fibrils are gelatinous or collagenous. Cells are few in both situations, and conspicuously fewer than in the small intestine.

The Generative System. Testicle.

There is great variation in the appearances met with and the only phenomencn common to all the species of animals examined is a tendency for the normal, intensely basophilic character of the spermatozoal head and the spermatid to be replaced in some instances by indifferent staining and in a few but undoubted instances by oxyphilic staining. The cellular contents of the tubules are somewhat contracted even under short exposure, but, with longer exposures and with survival, there may be great general disorganization and such cells as persist have a disorderly arrangement. Cells of Sertoli are usually recognizable and differ little from the normal. Spermatogonia, whether being small and

forming a definite and regular layer next the basement membrane (rat), or being larger and more irregularly disposed so that they are easily confused with spermatocytes (cat), usually show a diffusely and intensely basophil nucleus. Occasionally the chromatin is in prophase and occasionally the cytoplasm has disappeared and the nucleus is left naked within the cell. Spermatocytes vary widely in their appearance. The more peripherally placed cells usually show a moderately and diffusely stained nucleus of which the outlines are ill-defined. Occasionally ill-formed mitotic figures are present in numbers of the cells, but no examples of diaster stage or daughter nuclei have been found. As the middle of the tubule is approached nuclear staining in the spermatocytes becomes poor and the nuclei themselves become vesicular, and obviously the cell is undergoing degeneration. Spermatoblasts are rare and ill-formed as a rule, though the spermatozoal heads usually are arranged in normal fan-fashion and staining is intensely basophilic. Reference has already been made to staining of the spermatids. They are rarely found in any considerable numbers and in some animals were absent. Except in the frog spermatozoa are few, even when the exposure has been relatively short. With prolonged exposures and survival after exposure they tend to disappear, and the middle of the seminal tubules is occupied by oxyphil granular material in which are a few intensely basophil free nuclei. Under short exposures (rat) there is some evidence that spermatozoa may return after an interval. As has been said, the intense basophil staining of the head may be replaced by indifferent or even by oxyphil staining. Spermatozoal tails are always oxyphil, but their normal sharp definition may give place to granularity. The intertubular substance in frogs, rats, and rabbits is very scanty and consists of a rather loose connective tissue in which are capillary vessels and a few endothelial cells. In these animals it has no resemblance to endocrine gland. In the cat it is scanty and permeated by capillaries, but, owing to the presence of large polygonal cells with foam-like cytoplasm, well-defined outlines, and small round nucleus, it resembles congested cortex of adrenal. Throughout the entire series of animals examined there is little evidence of mitosis. When it occurs many deformed mitoses are present in the same specimen, but in numbers of animals the testicle presents no trace of mitosis whatever.

The epididymis itself is well preserved in all animals except the cat. The irregular sections of tubules are lined by a single layer of columnar epithelium provided with long cilia and the general excellent condition of the cells is in marked contrast with the poor condition of the testicular cells. In the cat and in animals exposed for prolonged periods, although definition of the nuclei in the columnar cells is impaired, desquamation of the cells does not occur and the cilia are usually recognizable. The lumen of the tubules may be empty or may contain degenerated spermatozoa and nuclear débris. Sometimes spermatozoal heads take the usual basophilic stain, but often they stain indifferently or are quite unrecognizable.

Ovary.

In rat, rabbit, and cat large corpora lutea in varying stages of development were the rule, and sometimes the organ consisted of little else.   Normal Graafian follicles were not found, but follicles in which an irregular ring of vesicular and highly degenerated nuclei surrounded a mass of structureless coagulum were common. In some animals the ovules were represented by round or oval spaces filled with coagulated amorphous material, possibly with central liquefaction, and in one rabbit, exposed for 48 hours and allowed to survive 7 days, haemorrhage into the ovule had occurred.   Usually the stroma was scanty, loose, perhaps much broken up, and under conditions of survival showed mucoid degeneration or vacuolation of cytoplasm and nuclei.   In rabbits and some rats, on the other hand, the stroma was voluminous, and, owing to the presence of many large polygonal cells with foam-like cytoplasm and small round nuclei, resembled cortex of adrenal.   The only difference in this interstitial (endocrine) substance that could be ascribed to exposure to irradiation or survival were oedema and haemorrhage in two rabbits surviving 7 days after a total exposure of 48 hours.

Fallopian Tube.

The lining epithelium is columnar and usually plicated or polypose.   Under different conditions of exposure or survival the cells may show vacuolation, mucoid degeneration or desquamation, perhaps after proliferation.   The nuclei may become irregular in shape and staining or vesicular.   The muscular coat is usually well preserved.

Lung and Air-passages.

In all the types of animal examined even a short exposure is followed by signs of congestion and exudation in the lung and alteration of the columnar epithelium lining the air-passages. The degree of change varies considerably according to the type considered, being greatest in cat and least in rabbit.   Under short exposures the capillaries are widely dilated and a few red blood corpuscles or a little granular débris is present in the alveolar spaces.   Sometimes there are small patches of collapse or consolidation alternating with emphysema, and with greater exposures or longer survival there may be a consolidation recalling lobar pneumonia in man, but patchy and devoid of polynuclear leucocytes.   The nuclei of endothelial cells covering the alveolar walls are usually vesicular and faintly stained, but under severe exposure they may be contracted or irregular in shape and stain intensely.   Desquamation of alveolar endothelium is never pronounced.   In the columnar lining of bronchi and trachea, though cilia may be present, there are usually signs of cell degeneration and desquamation, possibly associated with proliferation.   The most noticeable change, however, consists in the formation of mucus by way of goblet cells and mucoid degeneration of columnar cells.   In the rabbit, goblet cells and mucoid degeneration of columnar cells are wanting and free mucus is not found in the air-

passages, but the cells are swollen and on the point of desquamation. In the rat and frog the series of mucoid changes is moderate, and in the cat it is intense. The submucous tissue is oedematous and any mucous glands it contains are swollen bags of mucus. Peribronchial lymphoid tissue (rat) like spleen and lymphatic gland shows nuclear débris, absence of lymphocytes, and prominence of endothelial cells.

Thyroid and Parathyroid.

In the rat and rabbit there appears to be a slight but increasing diminution in the amount of colloid within the acini as exposure or survival is prolonged, but empty acini are rare. In the lining cuboidal epithelium the cytoplasm may be vacuolated and the nuclei contracted and deeply and diffusely stained, but often the epithelium is excellent. Some cases show a relatively large number of inflammatory cells in the interstitial substance and in one rat early calcification was noted. On the whole the histological condition of the thyroid is good, and in the cat remarkably good.

No changes whatever have been detected in parathyroid as the result of exposure to gamma rays.

Paraortic Tissue (rat).

As survival after exposure lengthens, the cytoplasm of the polyhedral cells becomes very finely granular rather than foamlike, and large lacunae, the former seat of fat globules are no longer found.

Lymphatic Gland.

There is great destruction of lymphocytes in rat, rabbit, and cat, and acellularity of the structure is a constant feature. The amount of nuclear débris in the glands of rabbits and cats is far less than in those of rats, and in all cases is at its maximum immediately after exposure and practically has disappeared by the third day of survival. This destruction of lymphocytes leads to acellularity of the gland tissue, but is accompanied in some cases by intense congestion or even haemorrhage. Hence the appearances differ in the glands of even the same animal. In most animals a few lymphocytes are found, but the great majority of cells is endothelial, small mononuclear, and plasma. Endothelial cells filled with red corpuscular débris are few immediately after exposure, unless it be prolonged, but the numbers increase with survival and often are a prominent feature. The general structure of lymphatic gland in advanced cases therefore consists of ill-defined, endothelial, germinal areas, amongst which are patchy masses of plasma cells, wide and relatively acellular channels, and numerous areas in which acellularity is considerable. The number of small mononuclear cells and of lymphocytes, the amount of nuclear débris, and the amount of blood present vary within wide limits.

Salivary Gland.

In rat, rabbit, and cat the serous variety of salivary gland was present, and in rat the mucous variety also. In the serous variety acini with fine basophil granular cytoplasm are intermingled with acini having relatively hyaline, oxyphil cytoplasm. No change can be affirmed with certainty in the acini though possibly oxyphil acini are fewer immediately after exposure and more numerous late in a survival period. In mucous salivary gland the mucoid change is advanced, the cells are swollen, their outlines distinct, the nuclei contracted, deeply stained, and pressed against the basement membrane. In the rabbit, survival 7 days after a total exposure of 48 hours is associated with an oedema or mucoid degeneration of serous salivary gland so considerable that the appearance closely resembles that of the mucous variety. The ducts are lined by a single layer of columnar cells. These cells swell and their nuclei become intensely vesicular and stain faintly under prolonged exposures, while the lumen of the duct contains some granular albuminous material or may be occluded by a definite plug of mucus.

Bone Marrow.

The bone marrow has been made the subject of a special examination by Dr. C. Price-Jones. Here it need only be stated that in rabbit and cat haemorrhages were numerous and the number of cells, both granular and non-granular, were greatly reduced. Such cells as remained were degenerated.

DISCUSSION OF RESULTS

It is impossible to discuss the results given in the foregoing pages in detail, but certain points merit consideration.

How far the changes met with in the organs and tissues generally are directly dependent upon the blood changes it is difficult to say. Nevertheless we have certain and pronounced effects of exposure to gamma radiation in (1) the rapid and profound destruction of lymphocytes noted even with relatively short exposures ; (2) the destruction of red blood corpuscles under more prolonged exposure ; (3) the signs of blood destruction and lack of regeneration in the bone-marrow ; (4) the modification of the normal relation between corpuscles and plasma resulting in the formation of non-corpuscular intravascular thrombus or fibrin formation within or outside the vessels. And however much gamma radiations may produce initial changes in any variety of tissue-cell, the evidence afforded by animals allowed to survive after exposure is that these changes intensify with time. It is reasonable to assume that this intensification depends in large part upon the supply of damaged blood to damaged cells. In other words, that late or secondary changes after gamma radiation are largely haemal in origin.

On the other hand it is possible that certain appearances are susceptible of other explanations. If the late phenomena were

entirely dependent upon antecedent blood changes all tissues of the body should be affected, approximately, to the same extent. This is far from being the case. Pancreas, salivary gland, thyroid, parathyroid, differ but little from the normal, in fact the microscopic sections of pancreas after irradiation are often better than those taken from a non-radiated animal. The explanation seems to lie in some cases in lower initial vulnerability, in others it may be that the rays impair the activity of an enzyme. With regard to the first possibility it is hardly necessary to insist upon the great variations in vulnerability of different kinds of cells by the rays. The lymphocyte and the polynuclear leucocyte, the renal cell in convoluted tubule and that in conducting tubule, the seminal cell of testicle and the columnar cell lining epididymis are extreme examples of variations in vulnerability, of which many intermediate degrees have been observed. Even with a single type of tissue such as striated muscle there is reason to believe that the vulnerability of one muscle may be greater than that of another. With regard to the second possibility one is on less certain ground, but the experimental impairment of certain enzymes by irradiation has been recorded.

That the primary changes in cells as the result of irradiation are physico-chemical is rendered probable by the alterations in shape that have been noted in nuclei of voluntary and cardiac muscle. Such alterations are consistent with variations in the water-content of the nucleus, and, inasmuch as the rays are known to break up complex chemical substances into simpler constituents, it is reasonable to suppose that they have split up in some degree the nuclear constituents into bodies of lower molecular weight, thereby raising the intranuclear osmotic tension. Under such conditions water would traverse the nuclear membrane and cause it to change from a rod-like to an oval shape.

Similarly the lipoid changes observed in striated muscle generally, in the cells of the convoluted tubules of the cat, and in cartilage cells probably represent distinct stages in the disintegration of protein into fat. The delicate balance between rays and cell composition is well shown by these observations. It is clear that not only does the composition of the renal cell in the convoluted tubule of the cat differ from that of the same cell in other species of animal, but that even in the cat the composition of the renal cell differs in convoluted and in conducting tubules. Possibly this fact should be correlated with the double origin ascribed to the renal tubules by many authors. On the other hand, in the adrenal there is some suggestion that gamma radiation may interfere with a normal formation of fat.

A similar change of a disruptive kind is seen in the extensive occurrence of mucoid degeneration in irradiated animals. Here again the importance of the cell constitution is indicated, for mucoid degeneration of cells—quite apart from formation of goblet cells—is much less intense in rabbits than in any of the other animals used in the experiments. The occurrence of an alteration in colloid of the thyroid is too uncertain for discussion.

The complete or nearly complete disappearance of cytoplasm

from some cells, leaving the nucleus relatively naked within the cell membrane, is an example of destruction in which the mechanism is not clear. The general absence of lipoid formation indicates that the solution is not to be sought in this direction, and there is no great evidence that the cytoplasm disappears by way of mucoid degeneration. The hyaline cytoplasm becomes finely and then coarsely granular and *pari passu* the granules disappear.

The products of cell destruction are rapidly removed and are only broken down to a point. The desquamation and excessive mucus formation in the intestine are simple examples, but the disappearance of large numbers of lymphocytes and the nuclear débris to which they give rise are unexplained, as is the absence of siderosis, considering the enormous destruction of red blood corpuscles.

The examples given above are relatively definite, but in other cases it is doubtful how far any appearance noted is an artefact, and alternatively how far any difference noted between the control and experimental animals is real. Thus in striated muscle a patchy translucency of the fibres appears to be pathological until it is found that normal muscle under the conditions of fixation and preparation adopted in the investigation is far more extensively translucent. On the other hand, normal cardiac muscle probably never shows translucency, whereas under conditions of severe exposure to gamma rays the appearance is noted in small, widely separated areas or even single muscle-fibres. It would probably be safe to conclude that the irradiation has altered the constitution of the contractile material on these grounds alone, but the occurrence of lipoid change in voluntary muscle confirms the view and carries it farther. In addition, there is no cause for surprise that voluntary and cardiac muscle under irradiation offer contrary results in respect of translucent fibres, for the lipoid change shows a similar contrast, being relatively frequent in voluntary muscle though it has never been observed in cardiac muscle. A similar difficulty arises in the case of appearances found in the sexual glands.

Further, the question arises how far a change observed in a given tissue is primary. The oft-quoted example of fat globules in the cells of the convoluted tubules of the cat serves here. Theoretically the globules might have been formed elsewhere and deposited in the renal cells during the exercise of renal function. That they were formed locally from the protein of the renal cells is rendered practically certain by the extreme nuclear degeneration of these same cells. It is inconceivable that cells in the condition of these renal cells could exercise a normal function.

In some instances it is possible to correlate the histological findings with clinical symptoms. Thus the diarrhoea, and particularly its mucous character, can be associated with the changes occurring in intestinal mucosa, the distension of stomach and gut by liquid and gas can be associated with changes found in the unstriated muscular coats, the excessive discharge of mucus

from the mouth with changes observed in the tracheal and bronchial mucous membrane and perhaps with mucoid changes in salivary glands. So, too, the impaired parturition seen in one cat may be associated with changes in the unstriated muscle of uterus, the haemorrhage from ears of one rabbit with alterations in composition of the blood and in the walls of larger and smaller blood-vessels, and it is remarkable that a somnolence comparable with that occurring in man with total suppression of urine occurs in cats in which there is profound alteration of the convoluted tubules of the kidney.

It is noteworthy that signs of cell division and regeneration have been nearly wanting. Whether the paired nuclei occurring in the liver of rabbits are to be regarded as evidence of amitotic division is uncertain ; they have not been found in other animals. Even in the testicle and intestinal mucosa, where normally cells in mitosis are relatively numerous, radiated animals show few such cells and the mitotic figures are deformed. Otherwise evidence of cell division is confined to a few instances in which the lining epithelium of ducts has undergone some proliferation before its desquamation. And lastly, though signs of recovery may be found, such recovery is slow in its onset and is lacking unless the exposure to gamma radiation be relatively short. With longer exposures many systems of cells show that they have received irreparable injury, and whether primarily or secondarily the animal dies as the result of irradiation.
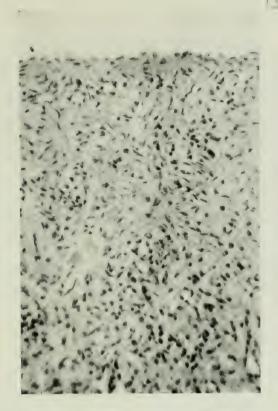
Fig. 1. Spleen of rat (Q 2), exposed for 46 hours and killed immediately. Above, the capsule is seen with its investing endothelium. The spleen is highly acellular ; the remaining cells are chiefly endothelial with conglomerate cytoplasm and contracted, irregularly stained nuclei. × 180.
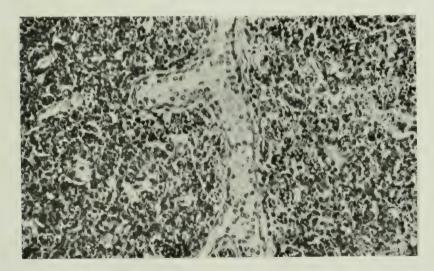
Fig. 2. Lymphatic gland of rat (Q 23), exposed for 16 hours and killed immediately. In the centre is a capillary containing many typical polynuclear leucocytes. The lining endothelium of the capillary is also well preserved. The gland tissue is much broken down, the nuclei are highly irregular in shape, and much deeply stained nuclear débris is present. × 180.

Fig. 3. Pectoralis major (human) from a case of mammary carcinoma exposed for 5 hours before operation. Running obliquely through the middle of the figure is a deeply stained muscle fibre in which numerous fine fatty globules are present. Little striation is visible. On one side of this fibre is relatively normal striated muscle, on the other are fibres the seat of translucent change. Frozen section, Sudan, Farrant. × 200.
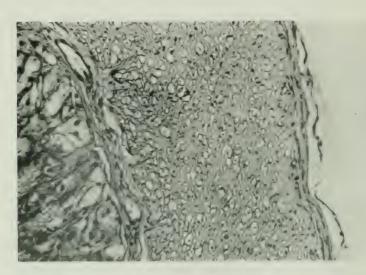
Fig. 4. Stomach of frog (Q 6), exposed for 21 hours, killed 3 days later. There is intense vacuolation in the contractile material of the inner muscular coat. The vacuole may carry a nucleus within it or on its wall. × 200.
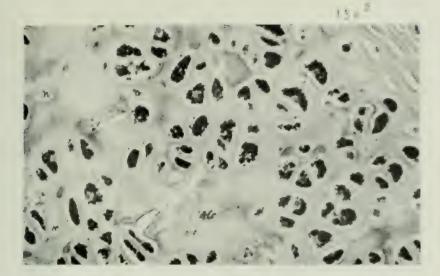
FIG. 5. Tracheal cartilage of rat (Q 24), exposed for 16 hours, killed 3 days later. There is marked fatty change in the cartilage cells, in many of which the nucleus is entirely obscured by the fat globules. Müller, osmic acid, paraffin. × 200.
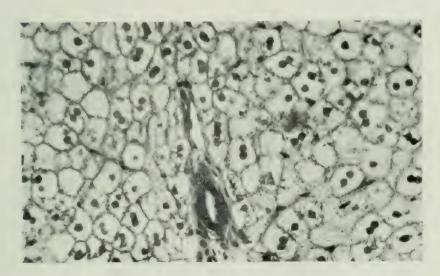
FIG. 6. Liver of rabbit (Q 14), exposed for 16 hours, killed 16 days later. The cytoplasm of the hepatic cells has disappeared almost entirely, leaving the nucleus naked in the middle of the cell. The cell membranes are sharply defined. The connective tissue surrounding the blood-vessel is in excellent condition. Twin nuclei are seen in many of the cells. From some cells nucleus has disappeared as well as cytoplasm. × 280.
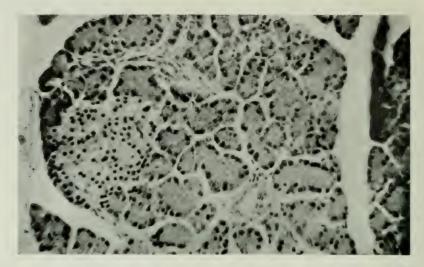
FIG. 7. Pancreas of rat (Q 2) from same microscopic section as Fig. 1. The pancreatic tissue and island of Langerhans show excellent preservation and staining. × 200.
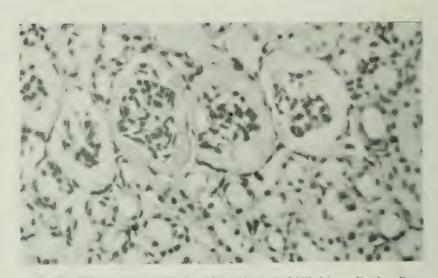
FIG. 8. Kidney of frog (Q 3), exposed for 6 hours and killed immediately. Four glomeruli are shown in which the glomerular space contains little or much coagulated exudation fluid. × 280.

FIG. 9   Kidney of cat (QF), exposed for 90 hours, death 50 hours later.   The convoluted tubules stain deeply owing to the presence of great numbers of fat globules.   The glomeruli and conducting tubules contain no fat.   The contrast is marked in the natural specimen.   Frozen section, Sudan, Farrant.   × 20.
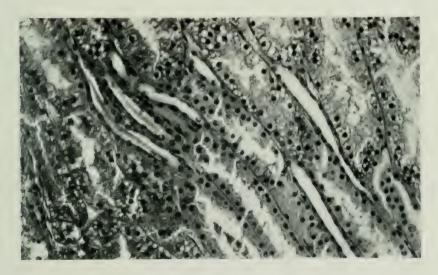
FIG. 10.   Kidney of same cat as Fig. 9.   The junction of two convoluted tubules with the corresponding conducting tubules to show the selective action of the rays. The great vacuolation of epithelium lining the convoluted tubule and the freedom from vacuoles of epithelium lining the conducting tubules are well shown.   The degree of irradiation of these contiguous cells must have been practically identical. × 200.

FIG. 11. Ileum of rat (Q 3), exposed for 24 hours, died 48 hours later. The external and internal muscular coats (the latter the seat of clefts and vacuoles), the stromal connective tissue with dilated lymph channels, and the large amount of mucus lying in the lumen of the gut, are well shown. The secreting elements have undergone extreme degeneration and desquamation, so that a few cells forming the blind ends of the tubules alone remain. × 200.

FIG. 12. Colon of rat (Q 20), exposed for 3 hours and killed 4 days later. The investing epithelium persists, but the columnar cells in the tubules are largely converted into goblet cells, from many of which the mucus has been discharged. × 200.
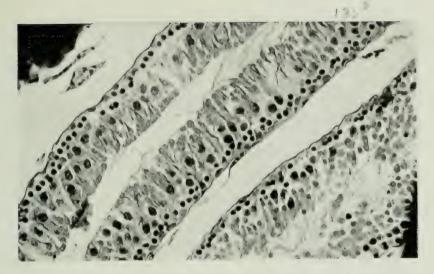
Fig. 13. Testicle of rat (Q 23), exposed for 16 hours and killed immediately. Longitudinal section of seminal tubule, showing cells of Sertoli, spermatogonia, spermatocytes, and numbers of spermatozoa. There is no evidence of mitosis, but the appearances differ little from the normal. × 200.
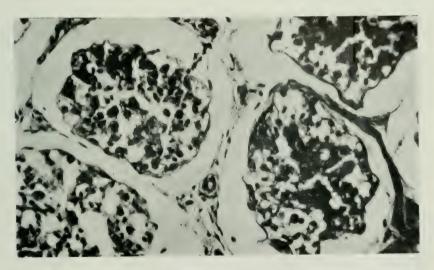
Fig. 14. Testicle of cat (QE), exposed for 95 hours, died 4 days later. Transverse section of seminal tubules. There is some contraction. The arrangement of the cells is disorderly and the nuclei found are large moderately and diffusely stained nuclei of spermatocytes or small round intensely stained free nuclei. There is no trace of mitosis and the cytoplasm of the cells is conglomerate. The intertubal material is scanty. × 200.
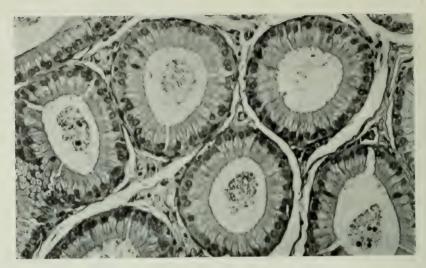
Fig. 15. Epididymis of rat (Q 23), exposed for 16 hours and killed immediately.
The tubules are well preserved, the lining columnar epithelium shows basal,
rather faintly stained, round nuclei, and a cytoplasm loose in the immediate
neighbourhood of the nucleus and denser towards the lumen, where it supports
long cilia. The tubules contain masses of spermatozoa with some free nuclei.   × 290.

Fig. 16. Ovary and Fallopian tube of Rat Q 22, exposed for 3 hours and killed
9 days later. The chief part of the ovary is occupied by large corpora lutea,
beneath one of which is a Graafian follicle see Fig. 17 . The Fallopian tube
shows a polypose epithelial lining.   × 10.
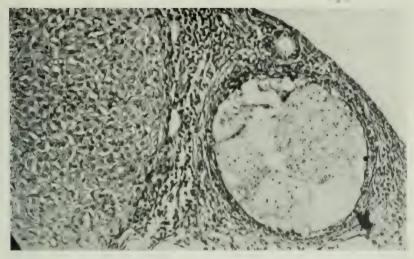
Fig. 17. Ovary of rat (Q 22). On the left is part of a corpus luteum with well-
marked luteal cells. On the right is a large Graafian follicle in which exudation
has taken place and the whole has become an amorphous coagulated mass with
some nuclear débris. Above is a small follicle of which the condition is apparently
identical. The stroma of the ovary between the corpus luteum and the follicles is
normal in appearance.   × 200.

Fig. 18. Tracheal mucosa of cat (QC), exposed for 64 hours, died 11 days later.
The ciliated epithelium is well shown, but the great majority of the columnar cells
have become converted into goblet cells heavily charged with mucus.   × 200.
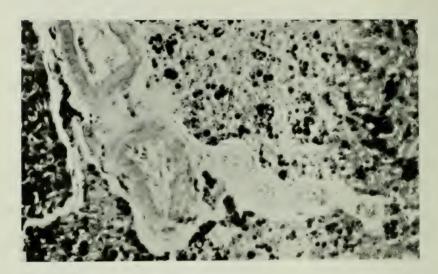
Fig. 19. Paraortic tissue of rat (Q 23), exposed for 16 hours and killed immediately. The section shows a large blood-vessel in which the muscular coat has become translucent and shows few nuclei. The paraortic tissue is the seat of patchy deposit of fat globules which vary greatly in size but agree in staining with osmic acid. Müller, osmic acid. × 200.

NOTE. The exposures were to 5 grammes $RaBr_2 \cdot 2H_2O$. Frogs and rats were exposed at 4 cm., rabbits and cats at 15 cm. ; in each case from the mid-point of the body in a crouching position. At 4 cm. the intensity of the radiation has fallen to 65 per cent. and at 15 cm. to 13 per cent. of the value at the face of the radium box. Unless otherwise stated the sections were hardened in 10 per cent. formol saline, embedded in paraffin and stained with haematoxylin and eosin.

4. HISTOLOGICAL EXAMINATION OF THE BRAINS OF ANIMALS EXPOSED TO THE GAMMA RAYS OF RADIUM

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CONTENTS

Material and Methods of Investigation.

The brains of 57 animals were sent including normal. These animals were frogs, rats, rabbits, and cats. In some cases the brains were fixed in formol saline and some in 96 per cent. alcohol. Of these 57 animals observations on 30 are recorded.

The methods employed for investigating the material were as follows. The tissues were blocked in paraffin and sections of 10 μ made. These were stained by Nissl, toluidin blue and eosin for the cells and Mann's method for eosinophil reactions. Ranke's Victoria blue method for glia and Van Gieson for general reactions. Frozen sections were also made from formalin hardened material for lipoid granules.

Most of the animals were killed by breaking the neck or cutting the carotid arteries; some died a natural death during the exposure or after some days following the experiments. Two sent that were killed by chloroform were rejected as unsuitable. No definite information regarding nervous trouble having arisen during or after the experiment was furnished. This had its advantages and disadvantages. On the one hand, had nervous trouble been noticed, an intensive investigation of one part of the brain might have been made and not of the rest. Undue significance might have been attached to changes in consequence. On the other hand, where there was *definite* and *reliable* change found it would have been of interest to have noted symptoms that could have been correlated with the same, e.g. the changes in the Purkinje cells. Still in these small animals it is extremely difficult to distinguish symptoms due to organic changes from those due to the nervous condition produced by the unfamiliar

surroundings in which they find themselves. Thus it would be extremely difficult to investigate nystagmus, ataxia or atonia in the limbs of the animal.

The changes observed were varying degrees of alteration or disappearance of the chromophilous basophile substance of the cytoplasm and some nuclear changes, but in these instances, where the length of time exposure was short, there was little difference from those observable in the brains of small normal animals.

Results of Microscopic Examination.

Rat (1).

48 hours' exposure to 5 gms. Ra Br$_2$, 2 H$_2$O.—death 2 days later.

Cortex. Few cells retain their pyramidal shape and show hyperchromatosis. A great majority of cells show swelling, have lost their pyramidal shape and the processes are indistinctly seen—especially their apical process. The nucleus is swollen and often eccentric. (Fig. 2.) This statement applies to all the different layers of pyramids and polymorphs. Exactly the same applies to the cortex of the neo- and archi-pallium. Examined with an oil immersion marked nuclear change is very apparent. The nucleus is so much swollen as to occupy nearly the whole of the body of the cell. The nuclear membrane is infolded and in the middle of the nucleus is seen the dark purple staining nucleolus. A number of small vacuoles is seen within the nucleus. The cytoplasm is almost devoid of basophile substance and consists of a network with only a thin incrustation of dust-like basophile substance.

Base of Brain. Cells show less marked changes.

Choroid Plexus. Cytoplasm of cells greatly diminished, nucleus swollen and deeply stained. Differentiation between nucleus and cytoplasm very indistinct.

Cerebellum. Layer of granules fairly well stained. Under low power the Purkinje cells appear to be well stained. Examined with an oil immersion it is seen that the chromophilous substance in some of the cells is on one side in the shape of a crescent ; in others the cells are diffusely stained a deep blue.

Large Cells in the Pons. The nucleus in many of the cells is swollen, the outline is irregular and merging into the trabecular network of the cytoplasm ; the nucleolus is very distinctly stained. The Nissl granules are not seen, only a fine dust of chromatin substance appearing on a network. Examined by an oil immersion these cells show no definite nuclear membrane, the nucleolus deeply stained and around is a dull purple irregular stained substance ; and surrounding this is an irregular space with fine threads traversing it and merging into the cytoplasm. This appearence is different to an ordinary peri-nuclear chromatolysis and is indicative of a physical as well as a chemical change. In some of the cells the nucleus appears to have been destroyed ; in none can the nuclear membrane be distinctly seen. This description applies to an average condition of the cells ; in other parts the cells show more advanced change, in others less, but nowhere can normal cells be discovered. (Figs. 1 and 2.)

Rat (2).

Exposure of 46 hours – killed.

Cortex. Under low power magnification the cells show less swelling and are better stained than those in Rat 1. It is quite obvious that there is a marked change in all the cells both in the neo- and archi-pallium. In the archi-pallium many of the cells show the basophile substance accumulated at one end of the cell.

Pons. Practically the same condition as Rat 1 except that the change is not so marked and there is a little more basophile substance in some of the cells.

Cerebellum. Cells of Purkinje show in some instances hyperchromatosis and shrinkage, others show an accumulation of basophile substance on one side, while others show a complete disappearance of basophile substance.

Rat (3).

24 *hours' exposure—died 2 days later.*

Cerebellum. The Purkinje cells show accumulation of basophile substance like a cap or a crescent at one side of the cells. The rest of the cell, especially opposite side to the crescent, is more or less disintegrated. The nucleus is stained a dull blue with nucleolus stained a deeper colour. The nuclear membrane, when it can be seen, is infolded, and there is obviously marked change in the nucleus as well as in the cytoplasm of the cell. Not a single normal Purkinje cell can be seen and no processes are visible. The granular layer appears rather faintly stained, but not much morphological change is observable. (Figs. 3 and 25.)

Pons. The cells show similar appearances to those described in **1** and **2**. Some of the cells appear to be entirely destroyed, nucleus extruded, in others the nucleus is on the surface and on the point of being extruded. The nuclear membrane is either not visible or very irregular in outline or swollen. (Figs. **4** and 27.)

Rat (4).

12 *hours' exposure—killed.*

Pons. Under low power magnification the cells show apparently little change and the outline of cells is more normal in appearance, especially does this apply to multipolars. The large cells, some of which as in microphotograph, show apparently fairly normal pattern of Nissl bodies and normal nucleus. In others, however, the Nissl bodies are not so distinctly seen and there is a tendency to hyperchromatosis ; in the immediate neighbourhood are large pontine cells which show commencing chromatolysis and disintegration of cytoplasm. The only cells which might pass for normal are the very large cells figured in photomicrograph no. 5, but these are relatively few. However, when examined under oil immersion, the apparently normal cells are seen to show marked changes. The Nissl granules are broken up into a fine dust, for the most part there are no Nissl granules on the processes ; the nucleus is swollen and clear, with an irregular outline, in fact there is a very considerable early change.

Cerebellum. Purkinje cells are the same as the other cases, but there is not quite so marked a directional change. (Fig. 6.)

Rat (5).

12 *hours' exposure—died 2 days later.*

Cerebellum. Purkinje cells show similar changes as in the other rats only the crescent is even more marked. (Fig. 7.)

Pons. The changes in the large cells appear to be more marked. The nucleus is not visible in most of these large cells and there is a marked chromatolysis. (Figs. 8 and 28.)

Rat (6).

24 *hours' exposure—killed.*

Cerebellum. The granules are less stained than the Purkinje cells, which is not usual. Many of the Purkinje cells show disintegration on one side of cell, with feeble staining and accumulation of basophile substance, but this is not so definitely directional as in other cases.

Pons. The cells have more normal appearances as regards shape and processes, but examined with oil immersion it is seen that they are uniformly stained a dull purple and the Nissl granules are not evident.

Cortex. Obviously marked change in cortical cells but pyramidal shape retained better than in Rat 3. Most of the cells show some nuclear and cytoplasm change as in Rat 3.

Rat (7).

Exposure 6 hours—killed.

Cerebellum. Low power, layer of granules faintly stained. Purkinje cells deeply stained, ' hyperchromatosis'. No definite evidence of crescent cap, whole cell stained a deep blue, nucleus quite distinct, processes not seen. Examined with an oil immersion the layer of granules appears swollen and very pale. Purkinje cells are oval in shape, very occasional process seen. In many cells no difference of nucleus from cytoplasm, in others only indistinctly seen. When nucleus is seen it is irregular in outline and nucleolus hardly visible, being of same stain as rest of nucleus.

Choroid Plexus. Choroid plexus quite empty of blood, epithelium appears shrunken and stained almost a uniform blue without any nuclear differentiation.

Pons. There are only a few of the motor cells which retain more or less their shape and processes; and these show a hyperchromatosis; they are scattered among cells which are more obviously changed morphologically. The greater number of cells have a large pale nucleus, the nucleolus not taking the basophile stain properly and the cytoplasm consists of an irregular network faintly incrusted with fine basophile stained dust. Many of the smaller cells appear to be disintegrated, leaving only the pale nucleus behind. There is no regularity in the disposition of the affected and slightly affected cells.

(This morphological change corresponds to what one finds in experimental anaemia). The small cells seem to be very markedly affected.

Rat (11).

Exposure 16 hours—killed.

Cortex. The surface of brain was covered with blood corpuscles (probably due to mode of death). Under a low power the cells show a more normal appearance in shape and presence of Nissl granules, but even the larger cells and all the smaller cells show some chromatolysis, but there is not the same degree of abnormal appearances observed in the other cases.

Rat (12).

16 hours' exposure—killed 48 hours later.

Cerebellum. The Purkinje cells do not show definitely the ' cap ' as observed in some of the other cases. The nucleus is swollen and irregular in outline in many of the cells. The cytoplasm shows a purple diffuse dust incrusting the network. The granular layer is comparatively poorly stained.

Pons. The large multipolar cells show marked changes, viz. swelling of cell; breaking off of processes; absence of Nissl granules and a network in the cytoplasm incrusted with basophile dust. Some of the multipolar cells retain their shape and processes, but do not exhibit normal Nissl granules and have a tendency to hyperchromatosis. The change in the cells has no regular group disposition.

Rat (13).

3 hours' exposure and killed immediately after.

Pons. Examined with a low power the large multipolar cells exhibit Nissl granules, but these do not appear quite normal, an early chromatolytic change is visible. (Fig 9.)

Examined with an oil immersion, nuclear changes are seen, and a majority of cells do not show normal Nissl granules. The processes are broken off, there is a distinct diminution of basophile substance and the cytoplasm consists of a network incrusted with fine dust of basophile substance with here and there remnants of Nissl bodies. (Figs. 9 and 26.) The small cells show more considerable changes of the same nature. (Fig. 9.)

Cerebellum. The layer of granules is better stained but not so well as normal. Purkinje cells show swelling of the nucleus, irregular outline, absence of Nissl bodies, processes not seen, no ' cap ' but tendency for basophile substance to clump. (Fig. 10.) Examined with an oil immersion there is evidence in some of the cells of directional change.

Rat (14).

3 hours' exposure—killed 3 days after exposure.

Pons. Under a low power magnification the large multipolar cells seem less affected that in Rat 13, as though some recovery had taken place (Fig. 11), but under an oil immersion there is evidence of considerable chromatolytic change in the great majority of the cells indicating that they would not recover. Some of the cells are covered with satellite cells.

Cerebellum. Under a low power magnification the Purkinje cells are not all equally stained, some are swollen and round as in Rat 13, others seem to retain their shape and the stain. (Fig. 12.) Examined with an oil immersion most of the cells are swollen and show swelling of the nucleus, breaking off and absence of processes and irregular network incrusted with basophile dust, but some are not swollen and retain their shape and are fairly well stained.

Rat (16).

3 hours' exposure, killed 9 days after exposure.

Not much difference to normal.

Rat (18).

3 hours' exposure and allowed to live 3 days before killing.

Cortex: Slight chromatolytic change.
Pons. No very marked change.

Rat (19).

Exposure 3 hours and killed immediately after exposure.

Rat (20).

3 hours' exposure and killed 4 days later.

No definite change.

Rat (22).

3 hours' exposure and killed 9 days later.

No definite change.

Rat (23).

Exposure of 5 minutes weekly for 12 course weeks.

Nothing of note .

Normal Rats.

Pons. Cells show condition very similar to those which have been described in animals with short exposures, but there is this marked difference, for groups of multipolar cells can be seen with normal tigroid pattern of Nissl granules. But the normal rat shows breaking up of the Nissl granules into a fine dust in the large cells.

This indicates that only the more marked changes observed in the multipolar cells of rats exposed to radium can with certainty be associated with the effects of the emanations.

Cat A.

Exposure 24 + 24 + 24 + 16 + 16 = 104 hours : died during last exposure.

Pons. Large multipolar cells show considerable chromatolysis and absence of the tigroid pattern of the Nissl granules. The nucleus has an irregular outline swollen and elongated in the long axis of cell. In the cytoplasm there are numbers of empty unstained spaces, rest of cell stained a diffuse blue. Condition might be the result of exhaustion. (Fig. 13 does not show much change, but when examined with oil immersion appearances are as in Fig. 31.) Compare with Fig. 33 (Normal Cat).

Cerebellum. Similar appearances in cells of Purkinje, swelling of nucleus, indefinite outline merging into vacuolated cytoplasm. The basophile substance appears to be more marked on one side of the cell ; it does not, however, form such a definite crescent as in the case of the rat. The layer of granules is faintly stained. (Fig. 14.)

Cat B.

Exposure 24 hours 10.2.20, 12 hours 13.2.20.

Pons. The pons shows the same appearance as Cat A except that the Nissl granules are to be seen, but there is the same vacuolation, swelling of nucleus and indistinct nuclear membrane. (Fig. 15.)

Cat D.

Exposure 6 hours flush to flank, 13.2.20, 24 at 15 cm. 29.6.20, died 12.7.20.

Pons. Large multipolar cells normal shape, Nissl granules seen, nucleus present but deficiency of basophile substance as shown by very light staining. (Fig. 16.)

Cortex. The pyramidal cells poorly stained in deeper layers, broken up, and many of them show numbers of satellite cells around. (Fig. 17.)

Cat E.

Exposure 16 hours at 15 cm. 19.2.20 ; 41 hours at 15 cm. 20.2.20 ; 20 hours at 15 cm. 23.2.20 ; 18 hours at 15 cm. 24.2.20. Total exposure 95 hours : died 29.2.20.

Pons. Some chromatolysis of cells, swelling of nucleus and vacuolation of cytoplasm. (Figs. 18 and 30.) The large multipolar cells seem to be somewhat shrunken and many exhibit no Nissl bodies, but a diffuse stain and vacuoles. Some of the cells show Nissl bodies as seen in Fig. 18.

Cortex. Examined with an oil immersion the Betz cells show hyperchromatosis and the Nissl granules are abundant. The pyramidal cells show a vacuolation of cytoplasm, absence of Nissl granules and swelling of nucleus. The apical processes are indistinctly seen ; it is difficult to state how far these conditions are due to pathological process directly caused by the emanations of the radium. (Fig. 19.)

Rabbit 2.

Exposure 16 hours at 15 cm. 1.4.20 : killed 7.4.20.

Pons. Considerable chromatolysis and disappearance of Nissl granules ; with vacuolation of cytoplasm. Large swollen nucleus with irregular outline and perinuclear chromatolysis. Some of the cells exhibit a normal outline, nucleus not increased in size but distinctly seen, nucleolus deep blue and Nissl granules indistinctly seen. (Fig. 20.)

Cortex. Pyramidal cells for the most part retain their shape and columnar arrangement, the apical process can be seen ; they all show a diffuse colouration of the cytoplasm with vacuolation and absence of Nissl granules. (Fig. 21.) The nucleus in many cells is swollen and irregular in outline.

Cerebellum. The Purkinje cells show a considerable degree of chromatolysis. No Nissl granules are observable. Some cells are almost devoid of basophile substance. A few cells show hyperchromatin at one pole. The granule layer is poorly stained as a whole.

Rabbit 4.

Exposure of 16 hours at 15 cm., 6.4.20., killed immediately after exposure.

Pons. Many of the large multipolar cells are apparently disorganized and show no Nissl bodies, and the cytoplasm is either vacuolated or disintegrated. The nucleus in some of the cells cannot be seen ; this may be due to its having become eccentric. (Figs. 22 and 32.)

Rabbit 8.

24 hours' exposure killed 9 days later.

Pons. Multipolar cells show the same appearances, irregular outline of nucleus and swelling, Nissl granules not clearly seen, vacuolation and diffuse staining in cytoplasm.

Rabbit 10.

3 exposures of 16 hours each on 3 consecutive days—killed immediately.

Pons. Multipolar cells show more marked chromatolysis and Nissl bodies less evident than in Rabbit 11. Nuclear changes similar but more obvious ; some of the cells show almost complete absence of basophile substance. (Fig. 23.)

Rabbit 11.

3 exposures of 16 hours each on 3 consecutive days—killed immediately.

Pons. Large multipolar cells have a normal Nissl pattern, rather faintly stained blue but not quite so brilliant a colour as normal. Nucleus network can be seen ; outline of nuclear membrane normal. This applies to one large cell (Fig. 24), but other cells in same group are not quite so normal in appearance, for the Nissl granules are beginning to break up. The outline of the nucleus is indefinite and irregular and merging into colourless space of cytoplasm. Some of these cells look shrunken. Many of the smaller cells are more markedly affected than the larger ones. (Fig. 29.)

Rabbit 15.

3 exposures of 16 hours at 15 cm.—killed on 7th day after exposure.

Pons. Under low power the shape of the multipolar cells appear to be normal, with nucleus in middle of cell.

Under oil immersion Nissl granules broken up in a great many of the cells and nucleus swollen. Just as marked a change in this rabbit as in numbers 10 and 11.

Summary of Observations.

Rats.

The histological changes in the brains of the rats are the most pronounced. There is a certain degree of correspondence in the histological changes and the length of time of exposure, although there is no definite relationship. On the one hand it seemed that an animal which had been subjected to a *short term* of exposure and allowed to live some days exhibited less alteration in the cells than an animal exposed for the same time and killed immediately after the experiment had ceased. From this it may possibly be inferred that recovery was taking place (*vide* Rats 13, 14, and Figs. 9, 10, 11, 12, and 26). On the other hand, animals which had been exposed *for long periods*, e.g. 12 hours, and died 2 to 3 days later, showed more marked cell changes than an animal with a corresponding time exposure and killed immediately after the experiment (*vide* Rats 4 and 5, Figs. 5, 6, 7, 8, and 28). The most obvious change which can be associated with the effects of exposure to the radium was observed in the Purkinje cells of the cerebellum ; a change not previously described, so far as we are aware, and therefore it may be assumed that it is directly due to the effects of prolonged exposure to the radium.

It was not observed in the cerebellum of rats with an exposure less than 12 hours. No definite evidence of a directional change was observed after 6 hours' exposure (*vide* Rat 7). There was not always a constant relationship between the degree of directional change and the length of time of exposure. In Rats 3, 4, and 5, the Purkinje cells show a crescent of basophile substance on one and the same side (*vide* Rats 1, 3, 4, 5 ; Figs. 3, 6, 7, and 25).

After these results had been observed it was ascertained that the rats had been fixed in such a position that the side of the brain had been exposed to the direct beam of the rays, and this may account for the fact that the basophile substance has been displaced in these large cells in the characteristic manner shown.

Cats.

It may be stated generally that compared with the rats the cell changes observed were slight and inconsiderable, even after very long exposure, e.g. 41 hours and after a succession of long exposures totalling respectively 95 and 104 hours (*vide* description, Cats A and B). The changes in the cells can only be definitely ascertained by examination with an oil immersion lens (*vide* Figs. 13, 14, 15, and 31).

Two animals lived some time after the exposure, Cats D and E (*vide* Figs. 16, 17, 18, and 19).

In Cat D the only characteristic change of importance is the large number of satellite cells seen around the poorly stained pyramidal cells of the cortex. It is probable that this change is indicative of a low state of vitality of these cells. Satellite cells were not seen in other cases as a rule. Possibly this may be due to the long period of time elapsing after the exposure and the effects on the general condition of the animal and its other organs.

Very little definite inference can be drawn from the observations in the brain of Cat 1; although as Fig. 19 shows there is some evidence of hyperchromatosis of one part of the cells possibly of a directional nature.

Rabbits.

The Purkinje cells of the cerebellum show marked chromatolysis but no definite evidence of a directional change as seen in the rat's brain. The chromatolytic changes in the cells of the brain of the rabbit, although the duration of exposure was less, are more marked than in the cat (*vide* Figures 20, 21, and 29, and descriptions of rabbit 2, also Figures 22, 23, 24, and 32, and descriptions of rabbits 8, 10, 11, 15).

General Conclusions.

The general and practical conclusions arrived at from these observations and from the fact that no gross nervous symptoms were reported even in animals that had lived days, weeks or

months after exposure, is that the central nervous system does
not suffer to any great extent in the larger animals such as cats,
even after prolonged exposure to 5 grammes of radium. This
may be due to the thicker protective coverings of the brain in
these animals.
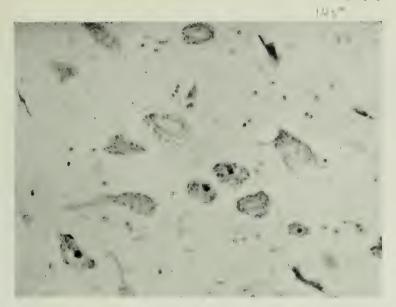
Fig. 1. Rat, No. 1. Exposed to 5 gm. of radium bromide for 48 hours ;
died 2 days later. Section of pons. × 400.

Fig. 2. Rat, No. 1. Section of cortex. × 400.

FIG. 3. Rat, No. 3. Exposed to 5 gm. of radium bromide for 24 hours; died 2 days later. Section of cerebellum. × 400. The four cells marked are shown on a larger scale in the colour drawing (Fig. 25).

FIG. 4. Rat, No. 3. Section of pons. × 400. The four cells marked are shown in Fig. 27.
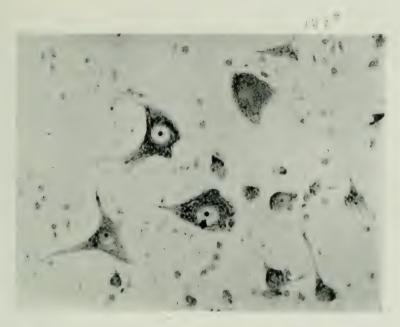
Fig. 5.   Rat, No. 4.   Exposed to 5 gm. of radium bromide for 12 hours;
killed immediately after.   Section of pons.   × 400.
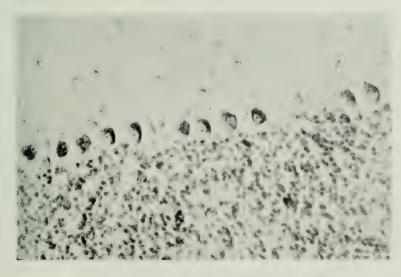
Fig. 6.   Rat, No. 4.   Section of cerebellum.   × 400.

Fig. 7. Rat, No. 5. Exposed to 5 gm. of radium bromide for 12 hours, 8/10/19; died during night 10–11/10/19. Section of cerebellum. × 400.
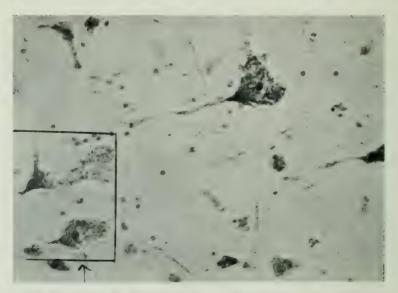
Fig. 8. Rat, No. 5. Section of pons. × 400. The three cells marked are shown in Fig. 28.
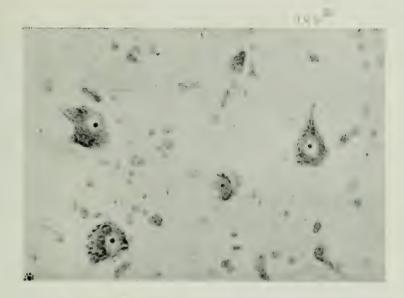
Fig. 9. Rat, No. 13. Exposed to 5 gm. of radium bromide for 3 hours; killed immediately after. Section of pons. × 400.
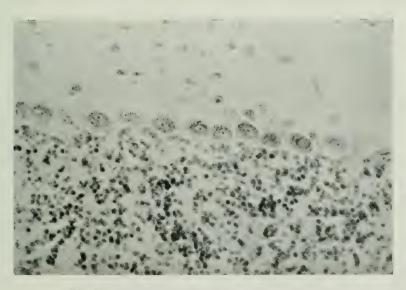
Fig. 10. Rat, No. 13. Section of cerebellum. × 400.
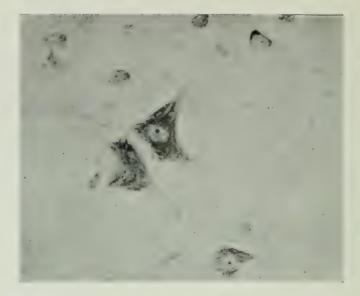
Fig. 11. Rat, No. 14. Exposed to 5 gm. of radium bromide for 3 hours; killed 3 days later. Section of pons. × 400.

Fig. 12. Rat, No. 14. Section of cerebellum. × 400.

Fig. 13. Cat A. Exposed for $24 + 24 + 24 + 16 + 16 = 104$ hours; died during last exposure. Section of pons. × 400. See also Fig. 31.
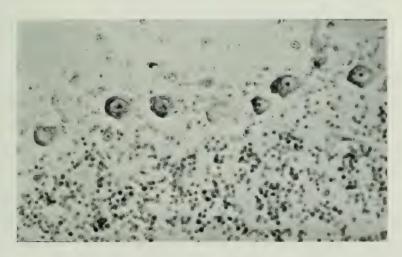
Fig. 14 Cat A. Section of cerebellum. × 400.
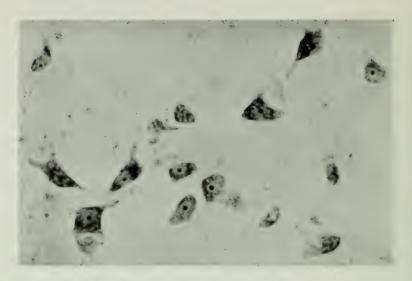
Fig. 15. Cat B. Exposed for 24 hours 10/2/20 and for 12 hours 13/2/20. Section of pons. × 400.
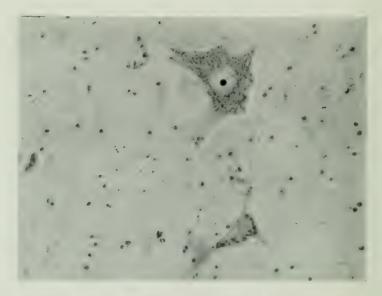
Fig. 16. Cat D. Exposed for 6 hours flush to flank 13/2/20 and for 24 hours at 15 cm. 29/6/20; died 12/7/20. Section of pons. × 400.
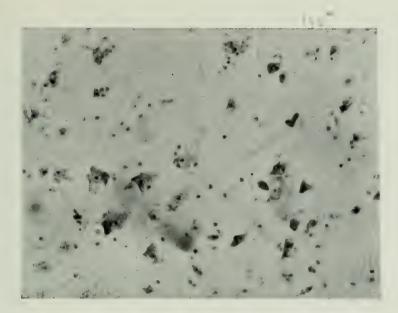
FIG. 17. Cat D. Section of cortex.   × 400.

Fig. 18. Cat E. Exposed for 16 hours at 15 cm. 19/2/20 ; for 41 hours at 15 cm.
20–22/2 20 ; for 20 hours at 15 cm. 23/2/20, for 18 hours at 15 cm. 24/2/20 ; died
29/2/20. Section of pons.   × 400.
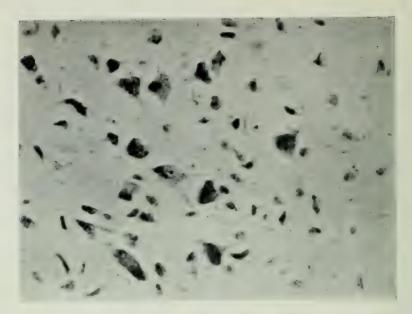
Fig. 19.   Cat E.   Section of cortex.   × 400.
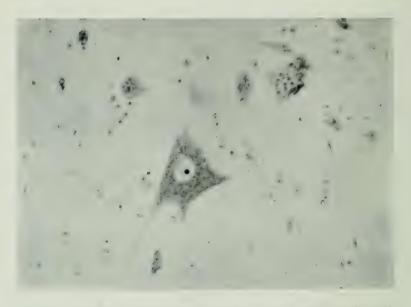
Fig. 20.   Rabbit, No. 2.   Exposed for 16 hours at 15 cm. 1/4/20; killed 7/4/20.
Section of pons.   × 400.
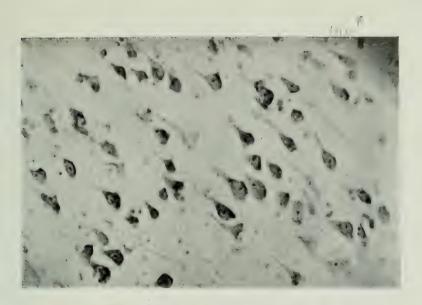
Fig. 21. Rabbit. No. 2. Section of cortex. × 400.

Fig. 22. Rabbit, No. 4. Exposed for 16 hours at 15 cm.; killed
immediately after. Section of pons. × 400.
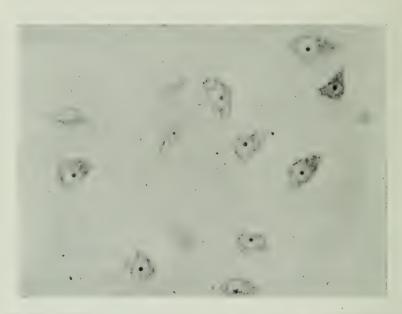
Fig. 23. Rabbit, No. 10. Exposed for 16 hours on each day for 3 consecutive days. Killed immediately after last exposure. Section of pons. × 400.
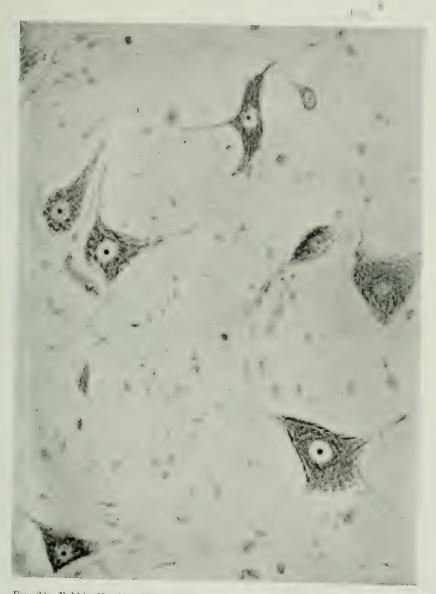
Fig. 24. Rabbit, No. 11. Exposed for 16 hours on each day for 3 consecutive days. Killed immediately after last exposure. Section of pons. × 500.
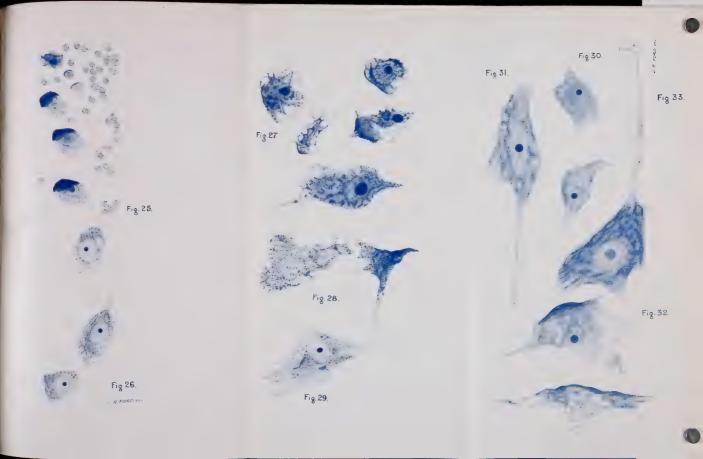
$\frac{1}{12}$ oil immersion ocular 6.

Fig. 30.

Fig. 31.

Fig. 33.

J. P. FORD del.

Fig. 32.

Fig. 25.

Fig 26.

R. FORD.

Fig 27

Fig. 28.

Fig. 29.

Fig 31.

Fig 30.

Fig 33.

Fig. 32

5. OBSERVATIONS ON THE EFFECTS PRODUCED ON THE BONE-MARROW BY EXPOSING RABBITS TO FIVE GRAMMES OF RADIUM BROMIDE

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These observations consist of two groups : (1) on the bone-marrow of rabbits exposed to the radium for 16 hours, (2) on the bone-marrow of rabbits exposed to the radium for 48 hours, (16 hours on 3 successive nights).

In the first group the animals were killed at different periods after exposure, viz. immediately after, or after intervals of 3, 5, 9, and 16 days. In the second group they were killed immediately after exposure or after an interval of 7 days. It was intended to kill these animals on the 9th day after exposure, but of two rabbits exposed one died suddenly from haemorrhage on the 7th day, and the other, which was killed after 7 days' interval, showed small haemorrhages into the internal organs, so that 7 days after such an exposure is probably near the terminal period. Each experiment was made in duplicate.

METHODS.

Glycerine films stained with Jenner (1) were prepared from the marrow of the femur, tibia, and rib. For the purpose of this account only the marrow of the femur has been considered, since the normal cell estimate of rabbit femur marrow has been previously determined. In each film 1,000 white cells were classified, and the number of nucleated red cells counted and classified simultaneously with the 1,000 white cells, is expressed in terms of the number of nucleated red cells present with 100 white cells, or the percentage of nucleated red cells to white cells.
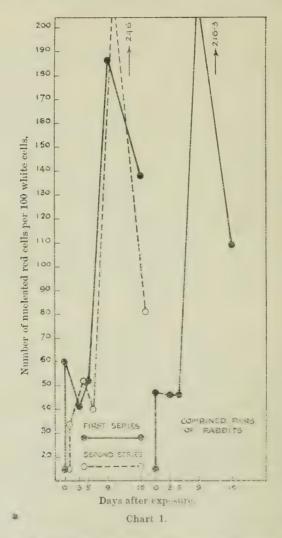
The classification of the white cells and nucleated red cells is the same as that adopted in my previous work on bone-marrow (*J. Path. & Bacteriol.* 1911, 15, 4). The results are given in detail in the accompanying tables and charts.

Paraffin sections were also made from each specimen of marrow. These were stained with Pappenheim or with Jenner. Detailed differentiation of the various white cells, according to the scheme adopted in the film preparations is not possible in these sections. Giant cells, granular cells and phagocytes are readily distinguished, but myeloblasts and other lymphoid cells cannot be differentiated with certainty, and the varieties of the nucleated red cells are not well defined. The chief value of the

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sections is the general information they give of the total number of cells in the marrow. Only broad estimates, however, can be made since the total and differential distribution of the cells is variable in different portions of the marrow. For this reason it often happens that sections seem to show different relative proportions of the various cells from those of the differential counts made from the corresponding films.

Chart 1.

(1) *Exposure to 5 gms. of radium bromide for 16 hours.*

Rabbits 4 and 5—killed immediately after exposure. The marrow was red throughout and soft at the extremities. Film preparations do not show any apparent changes in the morphology of the cells, which stain well and show neither vacuolation nor other signs of degeneration. Differential counts of the white cells vary only slightly from the normal, chiefly an increase in the

percentage number of the giant cells. A few large mononuclear phagocytes containing red cells and débris are noted.

The number of nucleated red cells per 100 white cells has risen from the average normal of 15 to 47 (Chart 1, Table 2), an increase chiefly due to normoblasts (Chart 2).

Sections show multiple haemorrhages throughout, and mostly a normal number of white cells, though in some areas they appear more scanty, especially in R. 5. The granular myelocytes seem to predominate. The nucleated red cells, especially normoblasts, appear more numerous than in normal marrow.

Rabbits 6 and 7 – killed 3 days after exposure. The marrow was red and firm throughout. In film preparations the cells mostly appear healthy and stain well, but a few myeloblasts contain vacuoles, and some granular myelocytes
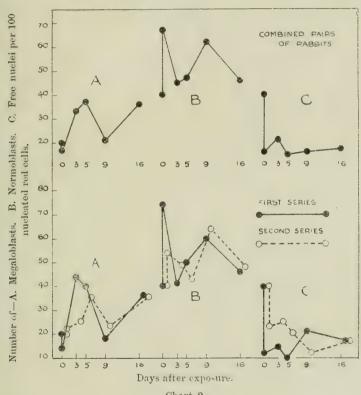
Chart 2.
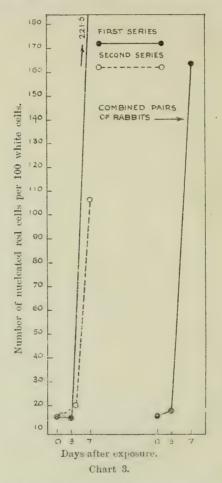
have faintly staining nuclei. Differential counts show a marked decrease in the number of granular cells and a corresponding relative increase in the number of the lymphoid cells, chiefly due to the increase in percentage number of myeloblasts. It is noted that whereas the majority of these cells show early granular myelocyte formation, a few show the early appearances of metrocytes. The percentage of giant cells is also further increased.

The number of nucleated red cells per 100 white cells is about the same as in R. 4 and R. 5, but the relative increase from the normal is chiefly due to megaloblasts (including metrocytes).

Sections are less vascular than those of R. 4 and 5 ; there is a large central haemorrhage and many small haemorrhages. The white cells seem in normal amount, though scanty areas occur in R. 7. The nucleated red cells appear more numerous than normal, especially megaloblasts in R. 6 and normoblasts in R. 7.

Rabbits 2 and 3—killed 5 days after exposure. The marrow was mottled and fatty in the centre; it was red at the upper and pink at the lower extremity. In film preparations the cells appear healthy and stain well; a few myeloblasts contain small vacuoles, and some myelocytes have faintly-stained nuclei. Differential counts show a further decrease in the percentage numbers of the granular cells, with a corresponding relative increase in the number of the lymphoid cells, due to an increase in the percentage number of the primitive cells. The giant cells are relatively decreased in number, and seem absolutely fewer in the sections. Some of the myeloblasts show granular myelocyte

Chart 3.

formation, but many show the early appearances of metrocytes. The picture of the nucleated red cells is much the same as with R. 6 and R. 7.

Sections show many scattered haemorrhages; R. 3 has a large central haemorrhage. The white cells, especially granular cells, appear fewer, especially in R. 2. The nucleated red cells seem in excess.
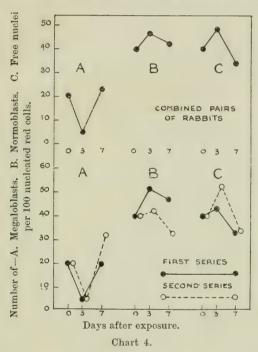
Rabbits 8 and 9—killed 9 days after exposure. The marrow was deep red and firm throughout. In film preparations the white cells are scanty, and many stain badly or show vacuolation. Granular cells are only rarely seen, differential counts showing only 7 per cent. of these cells, the lymphoid cells showing a corresponding relative increase (Table 2). The majority of the myeloblasts show early metrocyte formation. The number of nucleated red cells per 100 white cells is enormously increased, a total of 216 to every 100

white cells (Chart 1). This number is accounted for by the normoblasts, which show an increase of over 20 per cent. above their estimated normal percentage to other nucleated red cells (Chart 2). Sections show many small haemorrhages, and a marked decrease in the number of white cells. In some sections no granular cells were seen. Phagocytes are numerous. Nucleated red cells are in strong predominance.

Rabbits 13 and 14—killed 16 days after exposure. The marrow was firm, almost white, though pink to red at the extremities. In film preparations appearances resembling the preceding are seen. There are numbers of large mononuclear phagocytes often packed with red-cell débris. Differential counts show a tendency towards recovery. The granular cells have relatively slightly increased in number to 16 per cent., the lymphoid cells showing a corresponding relative decrease (Table 2). The myeloblasts are still relatively very numerous. Many of these cells are forming granular myelocytes, others show the early appearances of metrocytes. The number of nucleated red cells per 100 white

Chart 4.

cells is still high (Chart 1), though less than with R. 8 and R. 9, the increase being due chiefly to megaloblasts (Chart 2).

Sections show many small scattered haemorrhages, especially in R. 13. There is great deficiency of white cells. In many areas these cells are entirely absent. There is a marked predominance of nucleated red cells.

(2) *Exposure to 5 gms. of radium bromide for 48 hours (16 hours on 3 successive nights).*

Rabbits 10 and 11—killed immediately after exposure. The marrow was pale and firm. In film preparations the cellular picture varies but little from the normal. Some of the myeloblasts show granular myelocyte formation, but metrocyte appearances in the myeloblasts were not observed ; many of the myeloblasts are vacuolated. A number of large mononuclear phagocytes are present. Differential counts show great relative increase in the number of the giant cells from 0·9 to 8·0 per cent. The nucleated red cells are not increased in number relatively to the number of white cells ; with the exception of

a diminished number of megaloblasts and slight increases in the relative numbers of the normoblasts and free nuclei, there is no change from the normal picture (Charts 3 and 4, Table 2). The nuclei of many of the normoblasts and primitive erythrocytes are badly stained.

Sections show many scattered haemorrhages; in R. 10 there is a large central haemorrhage. The amount of white cells seems normal; in R. 11 at the centre of the section the white cells are absent, but towards the periphery they are in normal amount. There are numerous large mononuclear phagocytes. The nucleated red cells do not seem more numerous than in normal marrow.

Rabbits 12 and 15—killed 7 days after exposure. The lower portion of the marrow was pink and firm, the upper portion red and soft. Film preparations show similar appearances to those observed in R. 8 and R. 9, which were killed 9 days after exposure. The white cells are much reduced in number, and many stain badly and show vacuolation. The granular cells have practically disappeared, differential counts showing only 2 per cent. of these cells; the lymphoid cells show a corresponding relative increase (Table 2). There are numerous large mononuclear phagocytes. Many myeloblasts show metrocyte formation.

The number of nucleated red cells per 100 white cells is enormously increased to over 163 per cent. (Chart 3), and is chiefly accounted for by a relative increase in the number of megaloblasts (Chart 4). Sections show many small scattered haemorrhages. There are very few white cells, but nucleated red cells of all varieties are present in great numbers.

General Conclusions

The first impression obtained from consideration of the films, as recorded in the charts and tables, is that a single exposure of 16 hours to 5 gms. of radium bromide causes an active lympho-erythroblastic reaction in the bone-marrow, and that this effect reaches its greatest intensity between the 5th and 9th days after exposure. Exposure for 16 hours on three successive nights produces a similar effect, but the immediate reaction seems to be delayed by the repeated exposures. By about the 7th day after the triple exposure a most intense reaction has occurred, and is associated with the death of the animal.

Further consideration, however, offers another point of view. The erythroblastic reaction—the increased number of nucleated red cells per 100 white cells—would also appear if the absolute number of the white cells in the marrow was diminished. Examination of the sections shows that this is certainly the case. On the other hand, Chart 2, which gives the relative percentages of the different varieties of nucleated red cells, suggests that there is a definite increase in the percentage number of the megaloblasts and metrocytes, and that this most probably indicates erythroblastic activity. There is also the further evidence that so many of the myeloblasts show metrocyte formation, and do not seem to be forming granular myelocytes.

It is probable, therefore, that the results should be regarded as a combination of white cell destruction, diminished or inhibited formation of granular leucocytes, together with an exaggerated red cell production in response to the numerous haemorrhages and the phagocytosis of red cells which are prominent features of all the specimens examined. Until we acquire some means of estimating the total number of cells in the marrow, and some definite knowledge of the time occupied by the various transitions they pass through, it is not possible to explain more definitely the significance of the observations described above.

TABLE I.

A single exposure for 16 hours.

	Normal %	immediately after R 4 %	3 days R 6 %	5 days R 2 %	9 days R 8 %	16 days R 13 %	immediately after R 5 %	3 days R 7 %	5 days R 3 %	9 days R 9 %	16 days R 14 %
Primitive cells	29.5	23.1	21.2	46.7	37.8	27.1	19.6	25.1	30.8	43.0	28.9
Myeloblasts	15.5	17.5	34.5	16.7	38.0	41.4	14.7	30.2	22.8	42.9	41.5
Giant cells	0.9	1.3	4.1	0.9	6.0	1.9	4.3	3.0	1.4	2.4	2.2
Other lymphoid cells	3.7	3.4	3.0	5.6	12.6	10.2	3.0	3.6	2.2	2.4	7.7
Total lymphoid cells	49.6	45.3	62.8	69.9	94.4	80.6	41.6	61.9	57.2	90.7	80.3
Granular myelocytes	45.8	42.8	35.7	27.1	5.4	16.5	53.5	34.0	40.3	8.6	16.6
Polymorph leucocytes	4.6	11.9	1.5	3.0	0.2	2.9	4.9	4.1	2.5	0.7	3.1
Total granular cells	50.4	54.7	37.2	30.1	5.6	19.4	58.4	38.1	42.8	9.3	19.7
Megaloblasts and metrocytes	3.0	8.5	18.1	20.7	33.5	50.2	7.7	12.7	14.1	58.5	29.3
Normoblasts	6.5	45.2	17.1	26.6	112.6	62.9	18.2	24.5	17.3	158.2	38.5
Free nuclei	6.2	7.2	6.4	5.3	40.4	23.7	8.0	13.0	8.3	29.4	14.0
Total nucleated red cells per 100 white cells	15.7	60.9	41.6	52.6	186.5	136.8	33.9	50.2	39.7	246.1	81.8

TABLE II.
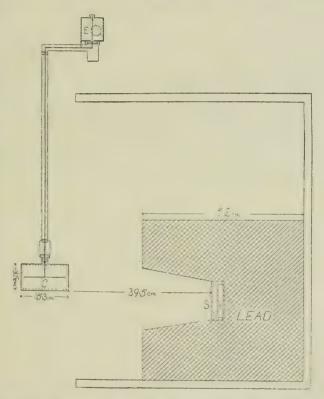
	Normal %	Single exposure for 16 hours. pairs of Rabbits. (Combined					Three exposures for 16 hours on 3 successive nights. (Combined pairs of Rabbits.)	
		immediately after. R4 + R5 %	3 days. R6 + R7 %	5 days. R2 + R3 %	9 days. R8 + R9 %	16 days. R13 + R14 %	immediately after. R10 + R11 %	7 days. R12 + R15 %
Primitive cells	29·5	21·3	23·1	38·7	40·4	28·0	19·3	42·3
Myeloblasts	15·5	16·1	32·3	19·7	40·4	41·4	16·9	37·1
Giant cells	0·9	2·8	3·5	1·1	4·2	2·0	8·0	4·9
Other lymphoid cells	3·7	3·2	3·3	3·9	7·5	8·9	10·3	12·9
Total lymphoid cells	49·6	43·4	62·3	63·5	92·5	80·4	54·6	97·2
Granular myelocytes	45·8	48·1	34·8	33·7	7·0	16·5	39·3	2·6
Polymorph leucocytes	4·6	8·4	2·8	2·7	0·4	3·0	6·0	0·1
Total granular cells	50·4	56·5	37·2	36·4	7·4	19·5	45·4	2·7
Megaloblasts and motrocytes	3·0	8·1	15·4	17·4	46·0	39·7	0·9	38·7
Normoblasts	6·5	31·7	20·8	21·9	135·4	50·7	8·3	69·3
Free nuclei	6·2	7·6	9·7	6·8	34·9	18·8	8·7	55·7
Total nucleated red cells per 100 white cells	15·7	47·4	45·9	46·1	216·3	109·2	17·9	163·8

6. ON THE AVERAGE RANGE OF β-RAYS IN DIFFERENT METALS

By G. A. Sutherland, M.A., and L. H. Clark, B.Sc.

THE present paper owes its origin to a suggestion of Professor Sir W. H. Bragg, that it would be worth while repeating some of his earlier γ-ray determinations with a larger quantity of radium now available. In particular the re-determination of

the average range of β-rays in different substances seemed of special value. By the courtesy of the authorities at the Middlesex Hospital, access to a considerable quantity of radium was arranged for the purpose of this investigation.

The theory of the method followed has already been explained by W. H. Bragg,[1] and it seems unnecessary to repeat it here. The experiments consisted in measuring the ionization in a lead chamber, exposed to very penetrating gamma radiation, when different linings were inserted into it.

The apparatus consisted of a cylindrical ionization chamber

[1] *Phil. Mag.*, Sept. 1910.

placed in the beam of gamma radiation from a brass box containing 3 gms. of radium bromide. The source S consisted of a number of small glass tubes containing the radium salt, which were distributed uniformly over a disc of 11·7 cm. diameter, and were screened by a lead disc 2 cm. thick. The tubes with their lead shield were contained in a flat, cylindrical brass box 13 cm. in diameter and 4 cm. deep. The ionization within the chamber C was measured by means of the electroscope E, which was very efficiently shielded from direct radiation by placing the radium container in a lead cubical block of 52 cm. side.

The diagram shows the apparatus with the ionization chamber in the end-on position, and gives the dimensions of the latter, which was made of lead, 0·49 cm. thick. It was arranged that the ionization chamber could be disconnected from the electroscope, and, by making one of its ends removable, the insertion of various metal linings into the chamber was easily effected.

It will be observed that the ionization chamber is arranged unsymmetrically with respect to the radio-active source S in order to prevent considerable ionization taking place within the stem connecting the chamber to the electroscope. As it was, 5 per cent. of the total ionization as given by the electroscope was due to that occurring in the stem.

The experiments of Bragg for the end-on position of the lead chamber have been repeated for linings of tin, zinc, iron, and aluminium. In addition a lining of copper was used.

TABLE I

Metal.	Mean thickness of lining in cm.	Ionization in C when broadside-on.	Ionization in C when end-on.	The earlier values.
Lead	0·49	100	100	100
Tin ..	0·16	67·2	68·2	68
Zinc ..	0·21	55·3, 54·4	52·5, 53·6	55
„ ..	0·35		54	
„ ..	0·42		54·9	
Copper	0·19	55 55·5	57·3 57·9	
„	0·25		57·1	
„	0·31		56·5	
Iron ..	0·25	55·3	56·6	
„ ..	0·155			54
Aluminium	0·26	49·6	48·2	
„	0·21			49

Table I shows the results obtained for the different linings when the ionization chamber was in the one case in the end-on, and in the other in the broadside-on positions with respect to the radium container. The second column gives the mean thickness of the lining, and the figures in the third and fourth columns are corrected for differences in volume, and for differences in the strengths of the γ-rays due to the differing absorptions by the various linings. For comparison, the figures in the fifth column are taken from the paper already mentioned,[1] and were obtained by using a source of only 5 milligrams of radium bromide. The agreement between the earlier and later figures is striking.

[1] loc. cit.

The theory of the experiment requires that the relative figures for the different linings should be independent of the thickness of the lining, provided that the initial thickness is sufficient to prevent the passage of β-rays originating elsewhere. The figures obtained for different thicknesses of the copper and of the zinc linings show that for these two metals, at least, this is approximately the case.

Table II

Metal.					Broadside-on. Ionization, I.	End-on. Ionization, II.	I/II.
Lead	..	..	..	..	268	202	1·33
Tin ..	..	..	..	..	140	107	1·31
Zinc	..	..	..	..	118	84·6	1·39
Copper	..	..	..	..	115	90.2	1·28
Iron	..	..	..	..	105	81	1·30
Aluminium		..	..	..	103	75	1·37

Table II gives the values of the ionization obtained for the various linings when the ionization chamber was (*a*) in the end-on position, and (*b*) in the broadside-on position. The last column gives the ratios of the ionizations for one and the same lining for the two positions. It will be seen that this ratio is approximately the same for all linings chosen which is in agreement with theory.

In conclusion, we wish to express our thanks to Professor Sir W. H. Bragg and Professor S. Russ for their kind help and suggestions.

Privy Council

MEDICAL RESEARCH COUNCIL

no. 63

Studies in
The Aetiology of Epidemic Influenza

BY

JAMES McINTOSH, M.D.

Medical Research Council.

INTRODUCTION

THE present Report gives the results of studies undertaken by Professor McIntosh during the epidemic of influenza in the autumn and winter of 1918–19 and later. The completion of some of the experimental work and some other circumstances have delayed the publication of the Report, and it should be understood that it was completed in its present form in 1920. The Council believe that the inclusion of the Report in this Series may be convenient to many other workers in the subject.

Visitations of influenza on a pandemic scale occur at relatively long intervals of time, and it is a matter of great importance that they should be studied from every point of view. The investigation of the true cause of the disease can, indeed, be pursued effectively only at such times, because the clinical conception of the disease 'influenza' is not defined with enough precision to allow us to say whether the minor inter-pandemic outbreaks or the innumerable sporadic cases of a similar affection are really instances of one and the same disease.

The Council have previously published other Reports upon work done during the 1918–19 pandemic, and they hope shortly to publish the results of more recent studies made within the past year. The results of the careful researches upon which Professor McIntosh now makes a full report—in supplement to an earlier preliminary communication—have been to lead him to the opinion that Pfeiffer's bacillus is the true cause of epidemic influenza, and he has marshalled the evidence in favour of this view with much force and skill. This is a view which, as is well known, was not held by all the writers in the previous Report published by the Council on the subject, and it may be well to take this opportunity of repeating that the Medical Research Council does not hold itself responsible for the scientific conclusions reached by the authors of reports which they may publish. The object of the Council

is to facilitate publication of the results of scientific work, leaving the evidence and the arguments offered by the authors to bring to other students appropriate conviction as to the justice of the conclusions reached. It is not likely that in this difficult subject, any more than in other directions of scientific progress, truth will be finally reached except through the clash of conflicting opinions.

MEDICAL RESEARCH COUNCIL,   27 *May* 1922.
    15 York Buildings,
      Adelphi,
        London, W.C. 2.

STUDIES IN THE AETIOLOGY OF EPIDEMIC INFLUENZA.[1]

By JAMES McINTOSH, M.D.

(From the Bacteriological Laboratory, London Hospital, and the Bland-Sutton Institute of Pathology, Middlesex Hospital, London).

CONTENTS.

1. INTRODUCTION.

THESE researches were undertaken with the idea of throwing some light on the aetiological agent of acute influenza and were mainly carried out during the recrudescence of the epidemic in the autumn and winter of 1918–19. Unfortunately at this period it was not possible to give as much attention to the problem as was necessary owing to other more urgent claims on one's time.

In order to make clear the line of argument pursued in this work, it is thought necessary to summarize here the conditions which must be fulfilled before a virus can be presumed as the cause of a disease. These are stated in the so-called Postulates of Koch. Koch did not actually tabulate any definite laws, but indicated the principles upon which the virus of an infective disease can be accepted as the cause. Briefly Koch's three main principles are as follows :

(1) The virus should be capable of being recognized in a large proportion of the cases of the disease, and preferably in relation to the chief lesions.

[1] Awarded the Liddle Triennial Prize, 1920. London Hospital Medical College, University of London.

(2) The virus should be living, i.e. should possess the power of indefinite propagation under suitable conditions. This can be demonstrated in two ways—(*a*) by passage through a series of animals; (*b*) by a similar passage on artificial media.

(3) The virus should be capable of reproducing the disease in animals.

The third is the final criterion by which a virus may be adjudged the cause of a disease. The term virus is used in a wide sense and must include the effects of any toxin produced by the virus. Thus, typical tetanus can be produced by the injection of a filtered culture.

In the application of the above tests to certain infections, and in particular in the case of Influenza, many difficulties arise. It may be pointed out that it is impossible to communicate certain human diseases to laboratory animals. In others a disease is produced but it does not show the typical lesions as seen in man, while the clinical phenomena of disease in animals cannot be judged with any degree of success.

In the case of influenza an additional difficulty arises from the fact that influenza up to the present has been a *clinical concept*, the diagnosis resting mainly on the presence of a catarrhal disorder of the respiratory tract which tends to assume epidemic and pandemic characters. Clinical methods are unable to distinguish between epidemic catarrhs due to entirely different microbes.

When the outbreak first appeared in the spring of 1918 doubt was expressed in many quarters as to its being true influenza. This was particularly the case amongst our troops in France, where the disease was given the name of P.U.O. (Pyrexia of Unknown Origin). But after a more careful survey of the symptoms and pathological lesions, the opinion gradually was formed that the epidemic was one of true influenza.

It is outside the scope of this investigation to go into the clinical features of the epidemic. But it is easy to see that the clinical features as described by Wirgman (1), Connor (2), and others are very similar to, if not identical with, those observed during previous epidemics (Thompson) (3).

The epidemic at its onset seems to have taken by surprise the bacteriologists as well as the clinicians, for the researches at this period are few and imperfect. The exact place and date when the epidemic first appeared is very indefinite. The Spanish origin of the outbreak is doubtful, although a large epidemic did occur in that country in the early spring of 1918. But an examination of the literature shows that local epidemics of apparently typical influenza were occurring in the British Army at home and in France even earlier than this, i.e. during the winter of 1916–17. Hammond, Rolland, and Shore (4), and Abrahams, Hallows, Eyre, and French (5).

The first large epidemic in the British Army occurred in May, June, and July, 1918, and then it was of a mild type. The symptoms lasted only a few days, and in many instances these were so

indefinite that the condition came to be known as 'three-day fever'. In all, some 226,615 cases were reported. In consideration of this and the relatively small amount of bacteriological work done it might be as well not to attach much importance to the findings at this stage of the epidemic.

In the British Army the disease recurred in November and December, 1918, when some 93,670 individuals were incapacitated from duty. The deaths are given as 5,555, which corresponds to 6·2 per cent. (7, 9).

In the Navy there was a severe outbreak in the Grand Fleet in May, when about one-ninth of the total strength was affected. Amongst the civil population the epidemic did not appear in any strength until June and July, although localized outbreaks were noted in May. In November and December there was a severe recrudescence of the epidemic with a high mortality (8). In other European countries very similar histories can be obtained.

2. Bacteriological Investigations.

The material examined was obtained from all types of influenza, and special care was taken that as little delay as possible should elapse between the collection and examination. The routine practice was to first make a film of exudate (sputum, pus, or lung juice), stain with Gram and counterstain with weak fuchsin or neutral red. By this means valuable information was obtained as to which type of bacteria predominated. Then, for the isolation of the various bacteria three different media were employed, namely, Matthews' trypsinized blood agar, serum agar, and ordinary agar (6). The first medium was used for the isolation of *B. influenzae*, for which it exhibits considerable selective powers. At the same time it inhibits many of the other bacteria which usually tend to overgrow the more delicate *B. influenzae*. It is unfortunate, however, that this medium is not always constant in these two qualities. The serum agar and ordinary agar provided a means of isolating the various Gram-negative and Gram-positive cocci present. A sufficient degree of dilution can be obtained with three tubes of each medium; one platinum loopful of the sputum or pus is rubbed over the three tubes in series, and the tubes then incubated over night. Occasionally the pus was emulsified in a few cubic centimetres of saline, and one drop of the fluid used to inoculate the tubes or plates in series.

For the preservation of the various strains of *B. influenzae* I have found boiled blood agar most suitable. This medium is easily prepared by adding 5 c.cm. of defibrinated blood (human, sheep, or rabbit) to 100 c.cm. of ordinary agar which has been melted and cooled to about 48° C., and then placing the flask in a water bath and gradually raising it to boiling-point. The flask is then removed after two or three minutes and the medium distributed into tubes or plates as desired. It is unnecessary to filter off the coagulum, which is a troublesome procedure. · *B. influenzae* grows luxuriantly on this medium, and will remain alive without being subcultured

for at least ten days, which is a matter of some importance when a number of strains are being studied.

Incidence of the various Micro-organisms.

As bacteria, in particular cocci, are present in any catarrhal condition, or for that matter in the healthy respiratory passages, a mere statement of their presence or absence would not be of much value. Thus, unless a particular organism is present in considerable numbers as indicated by a predominance of that type in the films and cultures no attention was paid to it. In many instances the film diagnosis gave a better index of the predominating type than did the cultures, which grew a great variety of organisms. This was not, of course, the case with regard to *B. influenzae*, as that organism is small and does not stain well, so that, unless present in considerable numbers, it is likely to be missed. The value of a selective medium like Matthews' is that it prevents the overgrowth of the more delicate *B. influenzae* by the other organisms. In addition the film preparations of the original pathological exudate present a fairly reliable means of differentiating between pneumococci and streptococci. In fact, in my hands I have found the morphological differentiation of pneumococci to be quite as good as many of the cultural tests now advocated.

The pathogenic microbes most commonly found in these influenza cases, either alone or in association with *B. influenzae*, were streptococci. pneumococci, staphylococci, and Gram-negative cocci meningococci, *Micrococcus catarrhalis*, and *M. pharyngis siccus*. It would appear that with the exception of *B. influenzae* the associated microbes tended to go in waves, as at one period one type predominated and at another another. Gram-negative cocci were more frequent in the earlier investigations and pneumococci towards the end of the epidemic.

An analysis of two groups of cases (see tables Nos. II, III) examined gave the following:

1. *Sputum from Acute Influenzal Broncho-Pneumonias.*

Predominating Organisms.

No. of cases.	B. influenzae.	Pneumo-cocci.	Strepto-cocci.	Staphylo-cocci.	Gram-negative cocci.
70	58	22	24	19	23
Per cent.	82·8	31·4	34·2	27·1	32·8

2. *Bronchial pus, lung exudates, &c., from series of post-mortem broncho-pneumonias examined during the epidemic period Oct. 1918 to April 1919.*

Predominating Organisms.

No. of cases.	B. influenzae.	Pneumo-cocci.	Strepto-cocci.	Staphylo-cocci.	Gram-negative cocci.
68 including 8 controls.	40	20	22	21	19
Per cent. 58·8		29·4	32·3	30·8	28·9

But when all controls and those cases where no signs were found definitely characteristic of the epidemic are excluded[1] the following figures are obtained:

No. of cases.	B. influenzae.	Pneumo-cocci.	Strepto-cocci.	Staphylo-cocci.	Gram-negative cocci.
48	36	13	16	10	13
Per cent.	75·0	27·0	33·3	22·2	27·0

A complete differentiation of the streptococci and pneumococci was not possible in this research, and distinction between the two was based on morphological appearances in films, on the character of the colony on serum agar and on certain fermentation reactions. Of these the fermentation of inulin was perhaps the most reliable. In a small series, in which most of the suggested cultural tests were employed, results were obtained which would tend to indicate that at least three types of pneumococci and two of streptococci were present. But further investigation was necessary to enable a quite definite statement to be made.

Incidence of B. Influenzae. In the epidemic period.

B. influenzae proved to be the most frequent pathogenic microbe present in the various pathological secretions of acute influenza. The relative frequency in the various types of cases and lesions as shown in Tables Nos. I, II, and III, is given below in tabulated form.

(a) *Early acute uncomplicated influenza* (posterior naso-pharyngeal swabbing).
   No. examined 17; *B. influenzae* present in 13 = 76·4 per cent.

(b) *Broncho-pneumonic types.* (Sputum.)
   No. examined 70; *B. influenzae* present in 58 = 82·8 per cent.

Post-mortem material.
   No. examined 48; *B. influenzae* present in 36 = 75·0 per cent.

Special series which included tracheal examination, naso-pharynx, &c.
   No. examined 16; *B. influenzae* present in 15 = 94 per cent.

Blood-cultures as a rule were sterile; on a few occasions strepto-cocci were found shortly before death.

Empyemata, 12 examined; *B. influenzae* found twice.

The close agreement between these groups is very striking, and is highly suggestive as to the aetiological importance of *B. influenzae*. Not only did this organism predominate, but in a large number of cases it was present in such numbers that pure growths, apart from a few other colonies, were obtained with great facility.

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[1] Nos. 5, 10, 16, 18, 20, 22, 23, 27, 32, 34, 35, 36, 38, 46, 51, 55, 56, 62, 64, 65 (Table III) did not present a typical influenzal broncho-pneumonia, while nos. 5, 32, 35, 36, 46, 51, 62, and 65 had been selected as controls.

10

TABLE I.

Pharyngeal Examinations of Acute Uncomplicated Influenza Cases.

(Nurses epidemic, 28th Oct. 1918.)

1.	Q.	Temp. 102° F.	Cultures gave only a few typical *B. influenzae* colonies.
2.	C.	Temp. 103° F.	No *B. influenzae* seen or cultivated—cultures showed a stout Gram-negative bipolar bacillus.
3.	K.	Temp. 102·2° F.	No *B. influenzae*, very few bacteria, only a few of the bipolar bacilli.
4.	T.	Temp. 100° F.	*B. influenzae* isolated, also a Gram-negative coccus (*M. catarrhalis*) and a stout bipolar bacillus.
5.	S.	Temp. 101° F.	*B. influenzae* isolated.
6.	S.	Temp. 101·2° F.	*B. influenzae* present, also Gram-negative cocci and a bipolar bacillus.
7.	G.	Temp. ?	*B. influenzae* present.
8.	M.	Temp. 103° F.	Numerous *B. influenzae* colonies with a few *Staphylococcus albus* colonies.
9.	C.	Temp. 102·5° F.	No *B. influenzae* isolated.
10.	B.	Convalescent case	*B. influenzae* present in considerable numbers.
11.	B.	Temp 101·5° F.	*B. influenzae*, also Gram-negative coccus present.
12.	I.	Temp. 101° F.	No *B. influenzae* found.

TABLE II.

Sputum of Acute Influenzal Broncho-pneumonias examined during the Epidemic Period Oct. 1918–June 1919.

No.	Initials.	Age.				B. influenzae.	Pneumococci.	Streptococci.	Staphylococci.	Gram-negative cocci.	Remarks.
1.	F. B.	29	...	...	...	+	...	...	...	+	
2.	S. N.	18	...	...	...	+	+	...	...	+	
3.	C. S.	20	...	...	...	+	...	...	+	+	
4	R. G.	40	...	...	...	+	...	...	...	...	Practically a pure culture.
5.	E. P.	28	...	...	...	—	+	...	...	...	
6.	G. G.	27	...	...	...	+	...	+	+	...	Pleuritic fluid contained only streptococci.
7.	P.	26	...	...	...	+	...	...	+	...	
8.	W.	40	...	...	...	+	...	...	+	...	Also *B. Friedländer*.
9.	B. H.	50	...	...	...	+	+	...	...	...	
10.	R.	45	...	...	...	+	...	...	...	+	
11.	E. H.	?	...	...	...	+	+	+	...	...	
12.	B. R.	?	...	...	...	+	+	...	...	...	
13.	W. P.	30	...	...	...	—	...	...	+	+	
14.	H. W.	17	...	...	...	+	...	...	+	+	
15.	D. M.	24	...	...	...	—	...	+	+	+	
16.	E. H.	?	...	...	...	+	+	...	+	...	
17.	C. G.	24	...	...	...	+	+	..	...	+	
18	W. C.	24	...	...	...	—	+	...	...	+	
19.	P. S.	25	...	...	...	+	+	...	...	—	
20.	Dr. X.	?	Broncho-pneumonia			+	...	+	+	...	
21.	W. G.	32	...	...	...	+	...	+	...	+	
22.	M. K.	36	...	...	...	+	...	...	—	+	

No.	Initials.	Age.	B. influenzae.	Pneumococci.	Streptococci.	Staphylococci.	Gram-negative cocci.	Remarks.
23.	M. G.	31	−	...	+	+	...	
24.	R. G.	23	+	...	...	...	...	Almost a pure culture obtained.
25.	A. D.	26	+	−	...	...	...	
26.	J. M.	42	+	...	...	+	...	
27.	M. S.	23	−	...	+	...	+	Microscopically positive, but medium overgrown with B. proteus.
28.	S. H.	45	−	+	+	...	...	
29.	L. A.	11	+	+	+	...	+	
30.	B. W.	32	+	+	...	...	...	Cultures on Matthews' medium gave almost pure B. influenzae.
31.	D. K.	25	+	...	...	+	...	
32.	H. F.	38	−	...	+	...	...	
33.	W. P.	45	+	...	...	...	+	
34.	F. R.	39	+	...	+	...	...	
35.	C. B.	25	+	...	...	+	...	
36.	S. G.	51	+	...	+	...	...	
37.	S. H.	26	−	+	+	...	+	
38.	J. M.	54	+	...	...	...	...	Culture almost pure.
39.	H. G.	40	+	...	+	...	...	Pleomorphic streptococcus.
40.	F. M.	35	+	...	...	...	+	
41.	R. H.	39	+	...	...	...	...	Culture almost pure.
42.	M. M.	32	−	+	...	...	...	
43.	H. G.	9	−	...	...	+	...	Sample of sputum appeared to be saliva only.
44	T. G.	19	+	...	...	...	...	
45.	K. M.	31	+	...	+	...	...	
46.	I. B.	22	+	...	+	...	...	
47.	E. C.	17	+	+	...	...	+	
48.	W. B.	17	+	...	...	...	+	
49.	S. I.	31	+	+	+	...	...	
50.	T. B.	?	−	+	...	...	...	
51.	S. C.	29	+	...	+	+	...	
52.	A. G.	27	+	...	...	...	...	T.B. present.
53.	S. W.	41	+	...	...	...	...	
54.	G. P.	27?	+	...	...	...	+	
55.	E. L.	?	+	+	...	...	...	
56.	D. C.	30	+	+	...	−	...	
57.	A. G.	32	+	...	...	...	...	
58.	I. P.	16	+	...	+	...	...	
59.	M. J.	28	−	...	+	...	...	
60.	K. Q.	26	+	...	+	+	...	
61.	W. M.	37	+	...	..	...	+	
62.	M. S.	28	+	+	+	...	...	
63.	I. S.	28	+	+	...	...	...	
64.	C. C.	22	+	+	...	...	...	
65.	F. H.	24	+	...	...	+	+	
66.	B. S.	20	+	...	...	...	...	Almost pure culture, T.B. present.
67.	B. H.	50	+	...	...	...	...	
68.	C. N.	38	+	...	...	...	...	
69.	W. R.	36	+	...	...	...	...	
70.	J. H.	22	+	...	+	...	+	

Table III.

Series of Broncho-pneumonias with Controls examined at autopsies, during the Epidemic Period Oct. 1918–June 1919.

			The lesions printed in italics were macroscopically suggestive of acute influenza.	B. influenzae.	Pneumococci.	Streptococci.	Staphylococci.	Gram-negative cocci.
Case.	Post-mortem No.	Age.	Macroscopic diagnoses.					
1	455	22	Septicaemia, bronchopneumonia, brown induration of lungs. Chronic rheumatic endocarditis. Recent miscarriage.	+	+	+	..	...
2	458	19	*Red consolidation of lungs and purulent bronchitis.*	+	...	+	...	...
3	462	29	*Subacute, purulent, bronchiectasis and organizing bronchopneumonia.*	+	...	...	...	+
4	463	23	*Bronchopneumonia,* chronic rheumatic endocarditis.	+	+	+	...	+
5	464	27	Slight pneumonia in back pressure lungs, chronic rheumatic endocarditis.	−	+	+	...	...
6	465	22	*Bronchopneumonia.*	−	...	+	...	...
7	474	2	*Bronchopneumonia.*	−	...	...	...	+
8	475	3	*Bronchopneumonia.*	+	...	...	+	+
9	472	27	*Bronchopneumonia,* acute and chronic rheumatic endocarditis.	+	...	...	...	...
10	467	9	Bronchopneumonia.	−	...	...	+	...
11	470	44	*Haemorrhagic, purulent bronchopneumonia.*	+	...	...	+	+
12	487	20	*Haemorrhagic bronchopneumonia.*	+	...	...	...	+
13	492	25	*Empyema: bronchopneumonia with abscesses.*	−	...	...	+	+
14	498	34	*Red pneumonic consolidation of lungs.*	+	+	...	...	...
15	494	40	*Purulent bronchopneumonia, fibrino-purulent bronchitis.*	+	...	+	...	...
16	502	28	Membraneous laryngitis, tracheitis, operation tracheotomy.	−	...	...	+	+
17	503	31	*Haemorrhagic, purulent bronchopneumonia with abscesses.*	+	...	...	...	+
18	504	1 3/12	Empyema, bronchopneumonia.	+	+	...	...	...
19	506	6	*Bronchopneumonia.*	+	...	...	...	...
20	508	36	Bronchopneumonia—Hodgkins lympho-granuloma.	−	+	...	+	...
21	523	6	Empyema, bronchopneumonia with abscesses.	−	...	+	+	...
22	525	6/12	Bronchopneumonia, catarrhal gastritis, enteritis and colitis—cultures overgrown with coliform bacteria.	−	...	...	...	...
23	531	5/12	Bronchopneumonia. Purulent meningococcal meningitis.	+	..	...	...	+
24	533	42	*Bronchopneumonia.* Syphilitic fibrosis with gummata of liver.	+	...	...	+	...
25	532	30	*Bronchopneumonia.*	+	...	...	+	...
26	534	39	*Non tuberculous and tuberculous bronchopneumonia.*	+	+	...	...	...
27	535	10	Pyaemia, pyaemic abscesses and bronchopneumonia, chronic purulent inflammation of sphenoidal air sinuses.	−	...	...	+	...
28	537	50	Bronchopneumonia.	−	+	...	...	...

Case.	Post-mortem No.	Age.	Macroscopic diagnoses.	B. influenzae.	Pneumococci.	Streptococci.	Staphylococci.	Gram-negative cocci.
29	538	52	Bronchopneumonia. Fibrino-purulent bronchitis.	+	...	...	...	...
30	540	36	*Bronchopneumonia, infected infarct of lung.* Pyaemia post-influenzal thrombosis of iliac vein.	+	...	+	+	...
31	544	20	*Pneumonia,* acute and chronic rheumatic endocarditis.	+	+	...	...	...
32	546	67	Bronchopneumonia, peritonitis, colostomy operation.	−	...	...	...	...
33	547	22	*Bronchopneumonia, empyema* — recent delivery.	+	...	+	...	+
34	556	42	Bronchopneumonia with abscesses, pneumococcal and syphilitic endocarditis, syphilitic aortitis.	−	+	...	...	...
35	560	48	Brown induration of lungs ; syphilitic aortitis and acute and chronic rheumatic endocarditis.	−	...	+	...	...
36	561	$1\frac{8}{12}$	Bronchopneumonia, chronic streptococcal abscess of neck.	−	+	..	...	+
37	562	53	*Haemorrhagic pneumonia, Pachymeningitis interna haemorrhagica.*	+	...	+	..	...
38	564	4	Fibrinous laryngitis, tracheitis and bronchitis, operation tracheotomy.	−	...	+	...	...
39	565	30	*Organized and unorganizing bronchopneumonia.*	+	...	...	+	...
40	566	4	*Bronchopneumonia.*	−	...	...	+	+
41	575	36	*Bronchopneumonia,* acute and chronic rheumatic endocarditis.	+	..	...	...	+
42	576	51	*Empyema abscess of lung, bronchopneumonia.*	+	...	...	..	...
43	581	30	*Bronchopneumonia,* old bullet wound of right chest.	−	...	+	+	...
	1919							
44	3	33	*Membranous laryngitis, and bronchitis organizing bronchopneumonia. B. diphtheriae* present.	−	...	..	+	+
45	60	25	*Septicaemia, Lobar pneumonia, Mitral stenosis,* acute and chronic rheumatic endocarditis.	+	...	+	+	+
46	70	$1\frac{8}{12}$	Bronchopneumonia.	−	...	...	+	+
47	72	32	*Septicaemia, pneumonia.*	+	...	+	...	...
48	73	7	*Early pneumococcal meningitis, bronchopneumonia.*	+	+	...	...	...
49	81	20	*Pneumonia, Mitral stenosis, acute and chronic rheumatic endocarditis.*	−	+	...	...	...
50	84	23	*Bronchopneumonia.*	+	...	...	...	...
51	85	2	*Slight muco-purulent bronchitis and bronchopneumonia,* tubercular meningitis with tuberculosis of lungs.	+	...	...	...	...
52	94	30	*Bronchopneumonia, organizing pneumonia. chronic bronchitis with abscesses of lung.*	+	...	..	...	...
53	88	24	*Pneumonia.*	+	+	+	..	...
54	90	57	*Bronchopneumonia.*	+	...	+	...	...
55	93	43	Tubercular meningitis.	−	...	+	+	...
56	91	65	*Bronchopneumonia* after operation for removal of bilateral ischial bursae.	−	...	+	...	...
57	92	20	*Bronchopneumonia,* cardio-vascular hypertrophy, chronic ascending nephritis —urogenital maldevelopment.	+	+	...	...	...
58	95	48	*Bronchopneumonia.*	+	+	.	. .	+
59	96	50	*Bronchopneumonia, tracheitis.*	+	+	..	. .	...
60	100	41	*Bronchopneumonia, serous meningitis.* Tetanus.	--	+		...	..

Case.	Post-mortem. No.	Age.		B. influenzae.	Pneumococci.	Streptococci.	Staphylococci.	Gram-negative cocci.
61	102	41	*Pneumonia*, mitral stenosis, chronic rheumatic endocarditis.	+	...	+	...	...
62	103	16	General fibrino-purulent peritonitis, chronic intussusception.	...	...	...	+	...
63	104	22	*Bronchopneumonia*, chronic rheumatic endocarditis and pericarditis.	+	+	...	...	...
64	105	65	*Haemorrhagic bronchopneumonia*, cardio-vascular hypertrophy.	−	...	...	+	...
65	106	40	Cerebral compression. Fibro-endothelioma of dura.	−	...	+	...	...
66	107	21	Pneumonia, brown induration of lungs. Mitral stenosis.	−	+	...	+	...
67	134	54	*Lobar pneumonia*, cerebral haemorrhage cardio-vascular hypertrophy.	+	...	...	...	+
68	146	36	*Bronchopneumonia*.	+	...	+	...	..

3. SEROLOGICAL OBSERVATIONS.

In view of the fact that the above bacteriological examinations show the constant presence of *B. influenzae* in the various lesions of the epidemic, the following serological investigations were undertaken with the idea of obtaining confirmatory evidence of the aetiological importance of this micro-organism.

It has been recognized for a considerable time that specific immune bodies against *B. influenzae* are to be found in the blood of convalescent influenza patients. These observations show that a considerable number of influenza patients have had their tissues invaded by *B. influenzae*. In the recent epidemic this has been repeated and confirmed by a number of workers, although a few have reported negative findings. Their observations are dealt with in a later part of the paper.

Complement Fixation Test.

In this test the blood serum of a number of convalescent influenza patients was tested against an antigen of *B. influenzae.*

Technique. The antigen was prepared by growing *B. influenzae* on a number of boiled blood agar plates over night. The luxuriant growth was carefully scraped off, weighed, and then emulsified in carbolic saline (9 per cent. saline plus 0·5 per cent. carbolic) in the proportion of 0·1 gm. to 100 c.cm. of saline. This antigen was then standardized against guinea-pig complement. Falling doses (0·25 c.cm. to 0·025 c.cm.) of the antigen were dropped by means of a Donald's pipette into the diluted guinea-pig complement (1 in 20), the volumes being adjusted so that the total volume in each tube was 1 c.cm. The tubes were then shaken to ensure complete mixing and incubated at 37° C. for one hour. At the end of this time 0·5 c.cm. of sensitized sheep's red corpuscles was added to each tube and the series replaced in the incubator. At the end of 20 minutes the largest quantity of antigen which just allowed complete haemolysis was noted and employed in the test proper.

In the actual test the total bulk of ingredients during incubation was 1·0 c.cm. as before, and falling quantities of the patient's serum (0·1 c.cm. to 0·0125 c.cm.) were employed. The serum was placed in the tubes, then the complement, and lastly the amount of antigen determined by the preliminary standardization. The tubes were then incubated at 37° C. for one hour and then 0·5 c.cm. of sensitized sheep corpuscles added (4–6 units of amboceptor). The tubes were then replaced in the incubator and the test read when the control sera gave definitely negative results. In the table below complete inhibition of haemolysis (i.e. positive) is indicated by 4, lesser degrees by a lower numeral.

Results. The following table shows that 12 out of 19 unselected influenza convalescents gave positive complement fixation tests :

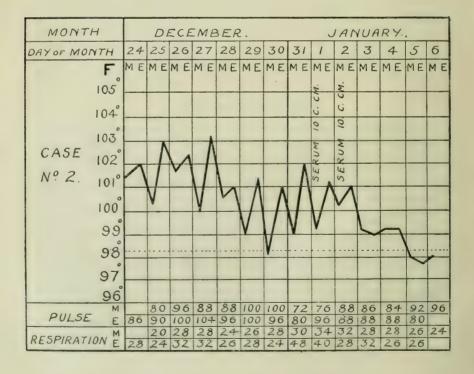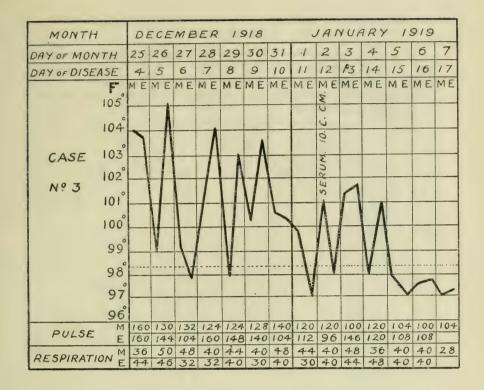| No.	Case.	Strength of Reaction. Amount of Serum.			
		0·1 c.cm.	0·05 c.cm.	0·025 c.cm.	0·0125 c.cm.
1	Ha.	4	4	3	3
2	Wh.	0	0	0	0
3	H.	4	4	4	4
4	Tu.	4	4	3	2
5	Control	1	0	0	0
6	Control	0	0	0	0
7	Go.	0	0	0	0
8	Fr.	4	4	2	0
9	Hu.	0	0	0	0
10	Gr.	4	4	4	4
11	Sy.	4	4	0	0
12	McM.	0	0	0	0
13	Hu.	3	0	0	0
14	Wa.	4	4	2	0
15	Po.	0	0	0	0
16	Bl.	4	2	2	0
17	Wh.	2	0	0	0
18	Do.	4	4	4	4
19	Fi.	4	4	3	0
20	Ro.	4	0	0	0
21	Pe.	·4	4	1	0
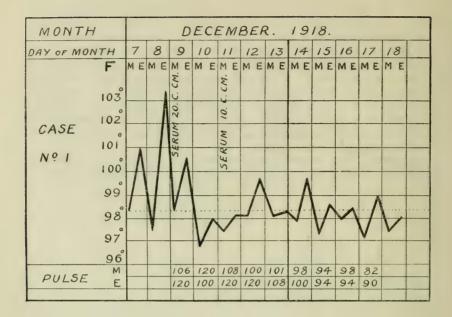
Agglutination Tests.

Agglutination tests were performed on the sera of the same patients. The test was carried out in small tubes or pipettes. The serum and the bacterial emulsion were then placed in a water-bath at 56° C. for one hour and the results read four to six hours later. Of 22 sera tested in this way 8 gave positive results in dilutions up to 1 in 100.
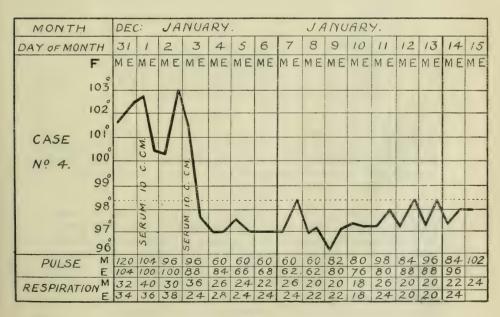
Therapeutic Effect.

The curative effect of the pooled sera of influenza convalescents was tested on a number of acute cases of influenza. In most of the cases 20 to 30 c.cm. were used with considerable benefit to the patient. In some the effects were immediate, but in others the effects were slower. In all instances the patients said they felt better after the injection. It has been claimed that this is a non-specific effect and can be produced by the injection of any normal serum. Whatever the exact mechanism is, there can be little doubt as to the good effect as the accompanying unselected charts show.

MONTH	DECEMBER. 1918.											
DAY OF MONTH	7	8	9	10	11	12	13	14	15	16	17	18
F	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

CASE No 1

Temperature scale: 103°, 102°, 101°, 100°, 99°, 98°, 97°, 96°

SERUM 20. C. CM. SERUM 10. C. CM.
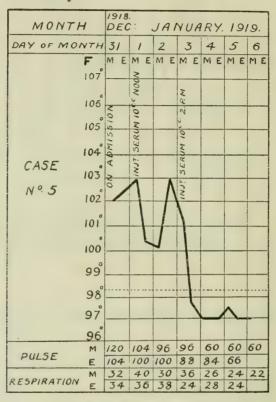
PULSE		7	8	9	10	11	12	13	14	15	16	17
	M			106	120	108	100	101	98	94	98	82
	E			120	100	120	120	108	100	94	94	90

MONTH	DECEMBER.							JANUARY.					
DAY OF MONTH	24	25	26	27	28	29	30	31	1	2	3	4	5 6
F	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E M E

CASE No 2.

Temperature scale: 105°, 104°, 103°, 102°, 101°, 100°, 99°, 98°, 97°, 96°

SERUM 10. C. CM. SERUM 10. C. CM.

PULSE		24	25	26	27	28	29	30	31	1	2	3	4	5	6
	M		80	96	88	88	100	100	72	76	88	86	84	92	96
	E	86	90	100	104	96	100	96	80	96	88	88	88	80	

RESPIRATION		24	25	26	27	28	29	30	31	1	2	3	4	5	6
	M		20	28	28	24	26	28	30	34	32	28	28	26	24
	E	28	24	32	32	26	28	24	48	40	28	32	26	26	

MONTH	DECEMBER 1918							JANUARY 1919						
DAY OF MONTH	25	26	27	28	29	30	31	1	2	3	4	5	6	7
DAY OF DISEASE	4	5	6	7	8	9	10	11	12	13	14	15	16	17

CASE Nº 3

PULSE M	160	130	132	124	124	128	140	120	120	100	120	104	100	104
E	160	144	104	160	148	140	104	112	96	146	120	108	108	
RESPIRATION M	36	50	48	40	44	40	48	44	40	48	36	40	40	28
E	44	46	32	32	40	30	40	30	40	44	48	40	40	

MONTH	DEC:	JANUARY.						JANUARY.								
DAY OF MONTH	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

CASE Nº 4.

PULSE M	120	104	96	96	60	60	60	60	60	82	80	98	84	96	84	102
E	104	100	100	88	84	66	68	62	62	80	76	80	88	88	96	
RESPIRATION M	32	40	30	36	26	24	22	26	20	20	18	26	20	20	22	24
E	34	36	38	24	28	24	24	24	22	22	18	24	20	20	24	

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4. Relation of the Micro-organisms to the Pathological Lesions.

It is, of course, necessary to correlate the bacteriological findings, in particular the incidence of *B. influenzae*, with the pathological lesions. For this purpose a short account of the gross and fine pathology of the tissues on which the bacteriological examinations were made is necessary.

MONTH	1918. DEC:		JANUARY. 1919.					
DAY OF MONTH	31	1	2	3	4	5	6	

		M	E	M	E	M	E	M	E	M	E	M	E	M	E
PULSE	M	120		104		96		96		60		60		60	
	E	104		100		100		88		84		66			
RESPIRATION	M	32		40		30		36		26		24		22	
	E	34		36		38		24		28		24			

CASE No. 5

Morbid Anatomy.

Epidemic influenza is essentially an acute inflammation of the respiratory tract with involvement of the lungs. The most striking feature is undoubtedly the marked engorgement of the trachea and bronchi, and the general congestion and oedema of the lungs.

Trachea.

The inflammation and engorgement of the trachea is usually marked along its whole length and spreads down into the bronchi. In early cases the trachea may contain a considerable amount of frothy, more or less blood-stained, fluid. The mucous membrane is often covered with a layer of greyish muco-purulent material, and in places shows sub-mucous haemorrhages. In a few the deposit of muco-purulent material is thick and adherent so that the condition might well be described as membranous.

CASE No. 6.

JANUARY.

DAY OF MONTH	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
PULSE M		100	100	98	60	64	72	70	82	96	80	88	80	86	76	80	72	68	62	82	80
PULSE E	124	120	102	98	44	72	68	71	86	80	80	80	82	80	80	74	74	80	84	80	84
RESPIRATION M	40	28	28	26	28	28	26	22	22	26	32	28	24	24	26	26	24	24	24	24	22
RESPIRATION E		32	30	28	32	28	24	24	26	24	26	26	22	22	28	22	22	24	24	22	22

SERUM 10. C.CM.

SERUM 10. C.CM.

Lungs.

The lesions met with in the lungs vary according to the extent of tissue reaction and the length of the illness. The lesions may, therefore, be regarded as more or less progressive although all stages may be found in the same lung. On broad lines the types of lesions may be grouped together as follows :

(1) Oedema and congestion with haemorrhagic areas and broncho-pneumonia.

(2) Broncho-pneumonia with bronchitis and peribronchitis.
(3) Gangrene and lung abscess.

Dealing with these changes in the order named, the first is certainly the most characteristic appearance observed at autopsies. In early cases the lungs are found to be voluminous and of a dark-red colour. The pleura is as a rule smooth and often shows numerous submucous haemorrhages. The lungs feel soft and of a jelly-like consistence, while firmer nodules may be felt throughout the lung. In some this has been likened to a mass of frogs' spawn. On section, the lungs are usually dripping wet and exude a serous fluid more or less blood-stained; in others the exudate appears to be almost pure blood. Scattered throughout the lungs are firmer, usually haemorrhagic, areas, looking at times like infarcts. Alternating with these and the emphysematous portions of the lung are the oedematous areas. The fluid in the latter may be coagulated, giving rise to a firm gelatinous oedema. A small amount of grey pus can at times be squeezed from the bronchi, but usually they only contain a frothy fluid. In such lungs the effect is evidently a direct intoxication of the capillaries, which become permeable, first to the serum and later to the blood cells. The patients in such cases may almost be said to have been drowned in the exudate.

In cases of longer standing where the intoxication has been less severe, the broncho-pneumonia is more in evidence. The broncho-pneumonic areas vary in appearance, and show some tendency to coalesce so that in some lungs the lesion is difficult to tell from a lobar pneumonia. In more advanced cases still the bronchitis and peri-bronchitis are more in evidence. At times the lungs have a peculiar slimy appearance and pus can readily be squeezed from the bronchi. In some the greyish pneumonic patches had given place to necrosis and abscess formation.

Other organs.

The liver and kidneys frequently showed extensive parenchymatous degeneration. The spleen on the whole did not show much change, unless there had been a septicaemic condition before death. Degeneration of the heart-muscle was only observed on one or two occasions.

Histopathology.

With the idea of ascertaining how the pathological process became evolved, particular attention was paid to the earliest changes observed.

The trachea and bronchi of those individuals who died of acute intoxication showed engorgement of the capillaries with oedema of the submucous layer, while here and there, chiefly round the blood vessels, accumulations of small round cells were to be seen. The epithelium of the mucous membrane in some cases showed some slight proliferation, in others the cells were necrotic and in some places shed. Bacteria were usually to be found in large numbers in the mucous exudate; on the surface of the mucosa and among the epithelial cells. In many instances only small Gram-negative bacilli (*B. influenzae*) were to be seen. In others numbers of

different cocci were to be found, mostly in association with *B. influenzae.* In the actual tissues, bacteria were observed chiefly in the submucous exudate, evidently having penetrated through the damaged epithelium.

Bacteria were also demonstrated in the lymphatic channels of the bronchi, in these cases *B. influenzae* was frequently found, either alone or in association with Gram-positive cocci (streptococci and pneumococci). The affected lymphatics were distended with a serous effusion, which might or might not contain cellular elements In most cases the cells present were chiefly lymphocytes. (Figure 7.)

In the lungs the earliest changes observed were dilatation of the capillaries, and a pouring out of a clear albuminous fluid, which in places completely filled the alveoli. Even at this early stage haemorrhages had occurred, and in places the alveoli contained numerous red cells. Apart from red cells the cellular elements were few in number, one or two catarrhal elements with an occasional leucocyte. The epithelium of the bronchial mucous membrane might show some slight proliferation, with swelling of the mucous glands. The lumen might even contain plugs composed of shed epithelial cells, mucus and a few leucocytes. In the alveoli at this stage bacteria of any kind were rare : their presence in the bronchi, however, has already been commented on. As the lesion progresses the picture becomes more typically that of a broncho-pneumonia. The alveoli are plugged with a cellular exudate, and even fibrin, while the same is true of the bronchioles. Bacteria are more numerous at this stage, and in a number of the cases examined *B. influenzae* was found. In many, however, there is such a variety of bacteria present that it is impossible to enumerate the various types.

Summary.

Macroscopic and microscopic examinations tend to show that acute epidemic influenza is primarily an acute inflammation of the respiratory tract with involvement of the lungs, giving rise to a haemorrhagic oedema and broncho-pneumonia. At a very early stage of the infection bacteria are to be found in the respiratory tract but are rare in the lungs. Later the lungs contain large numbers of bacteria. The type of bacteria found corresponded closely with the cultural results, while the close relation between the lesions and the distribution of the bacteria suggests that they play an important part in the aetiology of the condition.

5. Attempts to Produce an Experimental Disease and the Question of the Presence of a Filter-passing Virus.

The following experiments were undertaken with the idea of ascertaining whether or not acute influenza could be transmitted to laboratory animals and to monkeys. Filtered and unfiltered exudates were made use of in the inoculations, in order to determine the possible presence of any filter-passing virus. The results obtained are given in tabulated form.

TABLE IV.

Attempted Transmission to Animals.

A. Filtered Material.

Material.	Source of Material.	Date.	Animals.	Method of Inoculation.	Cultures.	Results.
1. Nasal washings	Two early uncomplicated cases in special wards.	6/11/18	Macacus rhesus (2), Rabbits (2), Guinea-pigs (2), Mac. rhesus (1), Hussar monkey (7)	Subconjunctivally 0·1 c.cm. Subcutaneously 5·0 c.cm.	Sterile	Nil, apart from a slight redness of the rabbit's conjunctiva.
2. Throat washings	Three acute early cases from the epidemic among the nurses.	20/11/18		As above, only 8·0 c.cm. given subcutaneously.	Sterile	Nil.
3. Lung juice	Three post-mortems showing characteristic lung changes.	15/11/18	Mac. rhesus, Dog-faced monkey, Rabbits (2)	As in no. 1.	Sterile	See note below.

B. Unfiltered Material.

Material.	Source of Material.	Date.	Animals.	Method of Inoculation.	Cultures.	Results.
1. Nasal and post-nasal secretion	Two acute uncomplicated influenza cases.	18/12/18	Mac. rhesus (2)	Direct swabbing of the nasal mucosae.	B. influenzae almost in pure culture.	Nil.
2. ,, ,,	One acute uncomplicated influenza case.	21/2/19	Mac. rhesus (2), Rabbits (2)	,, ,,	,, ,,	Nil.
3. Blood	Three acute uncomplicated influenza cases.	27/2/19	Mac. rhesus, Rabbits (2)	... ...	Sterile	Nil.
4. Freshly isolated pathogenic culture of B. influenzae	... ...	25/3/19	Mac. rhesus (2)	Direct swabbing of nose with thick emulsion of the culture.	... ...	Nil.
5. ,, ,,	... ...	31/3/19	Mac. rhesus (1)	Left nares plugged with gauze soaked in thick emulsion.	... ...	Slight discharge from nose, but no rise of temperature.
6. Insufflation experiment	... ...	4/19	Mac. rhesus (1)	Tracheal insufflation of B. influenzae emulsion.	... ...	Slight discharge from nose, but no rise of temperature.

In this experiment only the dog-faced monkey showed any effects. This animal 10 days after the inoculation developed a running at the nose and a temp. of 132° F., but an uninoculated monkey in the next cage had a bad cold. From this the animal got gradually weaker and died 34 days from the date of inoculation. A post-mortem examination showed accumulation of fluid in the pleural and pericardial cavities. The lungs showed no congestion, only a few consolidated areas. The spleen was slightly enlarged and showed a number of yellow areas. Bacteriological and histological examinations showed a recent septicaemia with miliary abscesses. The pericardial and pleural fluids were sterile. Blood cultures grew a coliform bacillus and staphylococcus. Passage inoculation (Mac. rhesus monkey) without result.

An analysis of Table IV shows that with one exception the inoculations produced no signs or symptoms which might be interpreted as an attack of influenza. The animals remained healthy even when observed over a long period of time independently of whether emulsions of sputum, lung juice, or cultures of *B. influenzae* were given.

The single exception mentioned above was a *Macacus cynomolgus* which ten days after inoculation developed a serous discharge from the nose and a rise of temperature. The animal gradually got weaker and died 34 days after it was inoculated. A postmortem examination did not show any characteristic lung changes, and a bacteriological and histological examination of the tissues suggested that death was due to a secondary septicaemia. Passage experiments were negative.

The above experiments show that under ordinary conditions, it is impossible to transmit epidemic influenza to laboratory animals or monkeys. Negative results were obtained no matter whether filtered or unfiltered material was employed. Thus not the slightest evidence in favour of the presence of a filter passing virus of the disease was obtained.

Pathogenicity of B. influenzae.

In Table IV mention is made of inoculations of emulsions of *B. influenzae* on to the respiratory passages of monkeys. But previously to this, inoculations both of emulsions of the bacilli and of whole cultures were made into guinea-pigs and mice to test the pathogenicity of the various cultures isolated. A considerable degree of variation was found in the cultures. Some were practically avirulent, most had only a feeble pathogenicity, while a few were found to be highly virulent.

At first tubes of ordinary broth containing pieces of fresh rabbit kidney were used, and of 24 to 48 hours' old culture 2–3 c.cm. were injected into the peritoneal cavity of a guinea-pig. Out of a large number of strains tested in this manner three cultures were found which regularly caused the death of the animal in 24–48 hours. The symptoms produced were fairly constant. The animal shortly after the injection appeared to be ill, was disinclined to move and remained in a corner of its cage. As a rule the hair was ruffled and the animal refused to eat. Within 24 hours it was distinctly ill, unsteady on its feet, and still refused to eat. There was usually diarrhoea with the passage of blood-stained mucus. Death followed in 24 to 48 hours, or might be delayed for 72 hours. A post-mortem examination showed some subcutaneous oedema, while the visceral and parietal peritoneal surfaces were pink from the numerous congested vessels. The abdominal cavity contained a considerable amount of a slightly opalescent fluid containing flakes of fibrin, while at times there was fibrinous deposit on the surface of the liver. The intestines were distended with gas and not infrequently showed petechial haemorrhages. The other organs showed no apparent change. Microscopic preparations of the sero-fibrinous exudate showed the presence of small Gram-negative diplo-bacilli

with longer forms which were at times almost thread-like; only a few leucocytes were to be found. In mice a very similar train of symptoms were produced, independently of whether whole cultures or emulsified bacilli were employed.

The toxicity of surface growths of *B. influenzae* can be judged from the following experiment. A weighed quantity of the bacilli from the surface of a boiled-blood-agar tube was taken, emulsified in saline, and then injected intraperitoneally into mice of about 20 grammes weight.

Mice.	B. influenzae strain.	Weight of bacilli.	Result 24 hours
1	88	0·004 gm.	Dead.
2	88	0·002	Dead.
3	88	C·001	Dying.
4	R.	0·004	Dead.
5	R.	0·002	Very ill—dead next morning.
6	R.	0·001	Ill—recovered.
7	155	0·004	Dead.
8	155	0·002	Dead.
9	155	0·001	Very ill—recovered.

6. Question of the Production of a Soluble Toxin by *B. influenzae*.

Certain of the toxic symptoms, in particular the temperature collapse, diarrhoea, congestion of the gut were suggestive of the action of a toxin. In fact this resemblance to certain of the anaerobic toxins is quite marked. It was, therefore, thought advisable to test the effects of filtered broth cultures. At first the filtrates of several days old cultures were employed but without much success. Later, by use of 24-hour old cultures in boiled blood bouillon, toxic effects could be produced in rabbits and guinea-pigs on intravenous inoculation.

In the case of rabbits (1,500 gm.) the toxicity varied considerably, but as a rule 5 to 6 c.cm. of the filtrate was sufficient to make the animal seriously ill. Not infrequently samples of toxin were obtained of which the above amounts, or even less, killed the rabbits almost immediately. At times death occurred after an interval of three or four days, while animals which appeared to be seriously ill recovered completely. Where death did not immediately follow the injection, the animal became depressed and crouched in a corner of the cage and refused food. At times actual collapse was observed. Within a few hours frequency of micturition with the passage of brownish coloured urine and slight diarrhoea was not uncommon, while next morning, and particularly so in young rabbits, numerous subcutaneous capillary haemorrhages were seen on the ears. As a rule, the condition described persisted for two or three days, and was followed by complete recovery. An animal killed at this stage showed, as a rule, subcutaneous haemorrhages on the body and considerable lung changes.

In the case of the guinea-pig the average lethal dose was 2 to 3 c.cm., but with some batches of toxin the lethal dose was 0·5 c.cm., or less, death occurring almost immediately or after some hours. Perhaps the most suggestive train of symptoms produced

in a guinea-pig were those seen in an animal where death was caused in four or five hours. Immediately after the injection the animals became collapsed, their hair ruffled, and their temperature subnormal. Some time later a discharge of frothy mucus was observed at the nose and there was slight diarrhoea.

Lesions.

In the injected animals lesions, often considerable, were always to be found when the illness had lasted for some hours. In many instances what surprised one was that such extensive changes could have occurred in such a relatively short period. As the changes observed in rabbits and guinea-pigs showed great similarity one description will suffice for both. It might be as well to indicate, however, that on the average the lung changes in the guinea-pig were the more marked. But in both animals the lung changes were so constant that one might rightly assume that the influenza toxin or poison had a definite selective action on the respiratory mucous membrane.

Macroscopic Appearances.

On opening the animal usually a slight but definite oedema of the subcutaneous tissues was to be seen. More constant, however, were subcutaneous petechial haemorrhages. In young rabbits, as already mentioned, these were most numerous in the ears. The lungs usually showed that several small areas, or more rarely that the whole of one lobe was involved. In the affected parts one noted slightly sunken red areas alternating with paler lung tissue, i.e. areas of collapse and emphysema. In some definite haemorrhagic spots were observed. On cutting into the lungs frothy mucus welled out, this at times was distinctly haemorrhagic in character. The trachea frequently contained a considerable amount of this frothy mucus, and its wall showed some congestion. The pleural cavity did not, as a rule, contain more than a very slight excess of fluid, while the same was true with regard to the pericardium. On one or two occasions small haemorrhages were seen on the heart-muscle.

The abdominal cavity, however, usually contained a considerable quantity of a clear serous fluid. The abdominal organs were all congested, and not infrequently showed petechial haemorrhages. The intestines were distended and at times showed fairly large subperitoneal haemorrhages. The kidneys were either normal in appearance or soft and enlarged with subcortical haemorrhages. The suprarenals, particularly in guinea-pigs, were often greatly congested and of dark red colour, just as is seen after diphtheria toxin.

Microscopic Appearances.

Lungs: In sections the affected parts were seen to consist of alternating areas of collapse and emphysema. The collapsed areas gave quite a typical picture of broncho-pneumonia, proliferation and desquamation of the alveolar and bronchial epithelium, infiltration

Toxic effect on guinea-pigs.

EXPERIMENT I.

Guinea-pig.	Filtered culture. Dose (intravenous).	Guinea-pigs about 400 grm. Result.
No. 1	2 c.cm.	Died in a few minutes.
No. 2	2 c.cm.	,, ,,
No. 3	1 c.cm.	,, ,,
No. 4	$\frac{1}{2}$ c.cm.	Survived.
No. 5	2 c.cm. (culture no. 129)	Survived.

EXPERIMENT II.

Guinea-pig.	Dose.	Result.
No. 1	1·5 c.cm.	Died almost immediately.
No. 2	1·0 c.cm.	Very ill, found dead next morning.
No. 3	0·5 c.cm.	Ill, but survived.

On rabbits the toxic effect was very similar except that for rabbits of 1,500–2,000 gm. 5 to 7 c.cm. was the average dose required to produce an immediate fatal result. If death did not occur over-night the animal usually survived.

It has been urged that this immediate lethal effect suggests that we are not dealing with a true toxin as these have definite incuba-tion periods. But recent researches on the toxins of the anaerobic bacteria of gas gangrene have shown that this is not always the case, and that toxins which produced true antitoxins can exercise an immediate lethal effect on intravenous injection.

Again, the effects on the suprarenals (congestion and haemo-rrhage) is very suggestive of a true toxic action, effects being very similar to that of *B. diphtheriae* toxin. The recent work of Cramer has shown that such effects on the suprarenal are produced by a number of specific bacterial toxins. The effects on the body temperature as indicated by the experiments given below also suggests a suprarenal effect. At first the temperature rises con-siderably and then falls again sharply if the animal is to die.

EXPERIMENT III.

Guinea-pig.	Dose of Filtrate.	Temperature.			
		12 p.m.	2.30	4.30	16 hrs. later.
No. 1	1·5 c.cm.	102·2	105·1	104·6	102·0
No. 2	1·5 c.cm.	102·0	105·0	104·2	101·8

EXPERIMENT IV.

This fever was almost entirely absent if a little antitoxin was given at the same time.

Guinea-pig.	Dose of Toxin.	Temperature.		
		$2\frac{1}{2}$ hrs. later.	$3\frac{1}{2}$ hrs. later.	5 hrs. later.
No. 1	2 c.cm. + $\frac{1}{10}$ c.cm. Immune sera	101·9	103·0	103·2
No. 2	,, ,,	101·2	102·2	102·4
No. 3 (Controls)	2 c.cm. without Immune sera	102·3	103·2	105·2

It has also been suggested that the toxic effects of these filtrates might be due to the presence of proteid degradation substances produced by the growth of the bacteria in the medium. But there

is no evidence so far that any substance of such a nature can produce these definite histological changes in the tissue. (Dale and Laidlaw (10), Abel and Kubota (11), and Fink (12).) Like true toxins the influenza poison is thermolabile, half an hour at 60° C. being sufficient to destroy the toxic action.

The crucial test, however, is whether an injection of the filtrate will lead to the formation of antitoxin or not. With this idea a number of rabbits were injected with increasing doses of the toxic filtrate over a period of from two to three months. Most rabbits thus treated were found to withstand at least one full lethal dose of the filtrate, while their sera *in vitro* had considerable power of neutralizing the filtrate. In fact, the sera of these rabbits had a weak but definite content of antitoxin against the filtrates of *B. influenzae* cultures as compared against normal rabbit sera.

Experiment V.

Rabbit.	Dose.	Result.
No. 1	7 c.cm. of toxin	No immediate effect found. Dead next morning with haemorrhages into gut and kidneys.
No. 2	7 c.cm. + 1 c.cm. of antitoxin	No symptoms at all.
No. 3	7 c.cm. + 1 c.cm. of normal rabbit serum	Very ill, recovered.

Experiment VI.

Rabbit.	Dose.	Result.
No. 1	6 c.cm. of toxin	Died in a few minutes.
No. 2	6 c.cm. + $\frac{1}{10}$ c.cm. of antitoxin	Soon collapsed, rapid breathing, and then slowly recovered.
No. 3	6 c.cm. + $\frac{1}{10}$ c.cm. of normal rabbit serum	No immediate effects, but some 30 minutes later breathing was slightly quickened and the animal rather restless, but this effect soon passed off.

From the above experiments it is evident that normal rabbit serum has a slight protective effect due to the presence of normal antitoxin. This is true of most toxin antitoxin experiments and to overcome this difficulty it is usual to use multiple doses of the toxin. But in the case of *B. influenzae* toxin this method of experimentation is not satisfactory, owing chiefly to the large doses necessary. This will be referred to later.

Experiment VII.

Guinea-pig.	Dose.	Result.
No. 1	2.5 c.cm. Filtrate + 0.5 c.cm. saline	Found dead next morning.
No. 2	2.5 c.cm. Filtrate + 0.5 c.cm. normal rabbit serum	,, ,,
No. 3	2.5 c.cm. Filtrate + 0.5 c.cm. Immune rabbit serum A	No ill effects.
No. 4	2.5 c.cm. Filtrate + 0.5 c.cm. Immune rabbit serum B	..

As already indicated the neutralizing effects of these immune sera against multiple doses of the filtrate was not satisfactory. This failure of the antitoxin to act against multiple doses of the

poison is rather disappointing. It suggests that the antitoxin is weak and that possibly, in addition. some other poison to which no anti-substance has been elaborated, is present in the filtrate in small amounts. Thus when multiple doses of the filtrate are employed the second poison is so increased that a toxic dose is present. This seems quite a likely explanation, as the hyper-immunized animals at times succumbed to three or four lethal doses of the filtrate. In addition, this immune serum when given along with the living culture can prevent an infection in the guinea-pig. Both culture and serum are given intraperitoneally.

The toxic filtrates, therefore, of cultures of *B. influenzae* present many points of similarity with true toxins. The only real objection is the failure of the antitoxin to act in multiple doses. It is hoped, however, that further experiments will elucidate this point. The therapeutic value of a good antitoxic serum in cases of acute influenza cannot be overestimated.

7. Relation of the Filter-passing Viruses to Influenza.

In the following section an attempt is made to summarize recent researches on the subject of filter-passing organisms so far as they concern the aetiology of influenza. The literature has been dealt with critically in order to ascertain to what extent these various claims have been substantiated. At the same time the opportunity is taken of placing my own experiences in line with those already published.

Filter-passing microbes as the cause of acute influenza have been described by a number of workers. The unanimity with which the claims have been brought forward alone carries considerable weight. but the trivial nature of most of the papers and the lack of experience in some of the investigators compels a certain degree of caution in accepting much of the work. This is particularly true when one recognizes the fact that the alleged discovery of an ultramicroscopic virus absolves the discoverer from the necessity of producing a description of the morphology of the microbe.

Kruse (13) appears to have been one of the first to advance the concept that influenza might be due to an ultramicroscopic virus. In 1914 as the result of one experiment he claimed that he had proved that common colds were due to a filtrable virus. The diluted and filtered nasal secretion from a case of acute nasal catarrh was placed in the noses of 30 members of his class. Fifteen of these developed colds and only one of the uninoculated controls. But it is obvious that if his assistant had a cold that this disease must have been epidemic at the time. This completely vitiates the experiments. In addition, the author made no attempt to show that he was dealing with a living virus. In fact, the same result could well have been produced by the irritant effect of an injection of weak formalin in the noses of persons exposed to infection. That colds are due to the *Aphanozoa coryzae,* as he termed his virus, has not been proved. Foster (14, 15) in America repeated and supplemented Kruse's work and claimed, in addition, that he had succesfully grown the virus. Cultures were obtained from the

filtered nasal secretions of ordinary colds. He employed Noguchi's medium and observed a cloudiness in the medium just above the haemolytic area in 24 hours' time. Smear preparations of the cloudy fluid after prolonged staining by Giemsa showed, under the microscope, minute coccoid bodies which were accepted as microbes. Further experiments by Dold (16) working in a German educational institute in Shanghai gave similar results in the case of Chinese students who lived together. But another experiment with hospital patients gave negative results. Dold also grew the virus in Noguchi medium; in the stained preparations nothing was found, but under the dark ground illumination numerous minute particles with active movement were seen. This culture, when placed in the nose of three individuals, produced in two increased nasal secretion and a slight cough. The author thus claimed that he had discovered the virus of common colds as an injection of the culture produced the characteristic lesion in man.

But any one who has worked to any extent with Noguchi medium will at once recognize that the growing cloudiness described is of little or no importance and is often to be seen in uninoculated tubes, while the multitude of minute particles found in the medium after prolonged staining or under the dark ground is only to be expected in albuminous fluids.

One is of opinion, therefore, that the description of these natural particles is sufficient to justify a complete rejection of the claims.

The above researches have undoubtedly influenced the trend of thought with regard to influenza, and for this reason have been given in considerable detail. Kruse (17) again in 1918 put forward the idea that epidemic influenza was due to an ultra-microscopic virus. v. Angerer (18) found similar bodies to those described above in cultures which had been made from the filtered blood of rats which had been inoculated with influenza sputum. No further experiments appear to have been done with this 'Virus'. Leschke (19) found particles with active Brownian movements in filtered lung juice of fatal influenza cases. He also attempted to transmit the disease to others by spraying the throat with the filtered lung juice. The first attempt was negative, but a later attempt in September 1918 was successful. The number of people operated on is not stated. No attempt was made to exclude the possibility of extraneous infection, and no attempt was made to show that he was dealing with a living virus. The same arguments can be used against Selter (20) who filtered the pooled throat washings of five cases of influenza and then along with his assistant inhaled the sprayed filtrate. Next day he had a cold and headache but no fever. His female assistant had some slight disturbance and slight fever, 37·6° C. But by no stretch of imagination could one accept the symptoms described as those of acute influenza.

Particles showing Brownian movement were described by Fejes (21) in ascitic broth which had been inoculated with filtered influenza sputum. A series of monkeys were inoculated with his cultures, injections of heated culture being used as controls. Four monkeys which had received the unheated culture developed an illness, and died in from nine to twenty-four days. The controls

remained healthy. Post-mortems revealed in these animals a condition of haemorrhagic sepsis, haemorrhages being found in all the tissues of the body. No mention is made of histological or bacteriological examinations, one is therefore at liberty to assume that his filters were not so bacterium-proof as he believed, and no attempt is made to exclude ordinary bacteria as the cause of death in his positive experiments. Prell (22) described granules in sections of influenza lungs which he called '*Aenigmoplasma influenzae*', and claimed that they were the cause of influenza.

In France Nicolle and Lebailly (23) came to the conclusion that influenza is due to a filtrable virus which is to be found in the respiratory tract but not in the blood. Their experiments are not very convincing. Seven observations were made on man and on monkeys with three positive results. Filtered influenza sputum was inoculated subconjunctivally into a monkey which later showed depression, wasting, and diarrhoea. The same filtered sputum was inoculated into a man subcutaneously, who six days later developed what appeared to be the classical signs of influenza. In another man a similar injection produced a mild influenza. The other experiments were negative. As with the German workers the above authors made no attempt to show that their virus was anything other than the irritant effect of the sputum injection, an effect which might have been produced by sputum from a non-influenzal case.

In Britain, Bradford, Bashford, and Wilson (24) claimed to have cultivated the filtrable viruses of a number of infections including influenza. Their work, however, owing to the criticisms of Arkwright (25) appears to have been withdrawn.

Gibson, Bowman, and Connor (26) working in the Army laboratories in France carried out a large number of experiments, and on those claimed somewhat similar findings in the case of influenza. Owing to the unfortunate death of one of the workers the work was not completed. They also noted the spreading cloudiness in the Noguchi tubes which they inoculated, and carried on the ' Virus ' in series. They state that two *Macacus rhesus* monkeys inoculated subconjunctivally and intravenously with filtered influenza sputum developed on the second and seventh day an acute illness which was considered to be experimental influenza. Autopsies showed a haemorrhagic exudation in the lungs and otherwise comparable to lesions of influenza. Coccoid bodies were recovered in culture from the kidneys of the animals, and on inoculation reproduced the disease. They failed to grow these bodies from the kidneys of normal animals.

The coccoid bodies described by the above writers are without much doubt similar if not identical with those described by other workers as the filtrable virus of influenza. Their descriptions of the experimental lesions are not always clear, and with regard to passage experiments the only definite statement is that the animal's lungs showed some haemorrhagic areas. I think, however, that these writers paid too much attention to the lesions found in monkeys, animals which we know are extremely liable to inflammatory lung conditions of all kinds.

Completely negative filter-passing experiments have, on the other hand, been obtained by a number of workers, and in all probability many more have refrained from publishing purely negative results. Thus Lister and Taylor (28) working on volunteers obtained uniformly negative results. These volunteers were removed to an island 500 miles away where there was known to be no influenza, and where the possibility of spontaneous infection could be eliminated. Nasal washings from acute influenza cases, both filtered and unfiltered, were introduced into the nasopharynx of these men and also into monkeys. Those men receiving the unfiltered material developed a typical influenza, while the filtered material produced no effect on man or monkey. Using extracts of lungs from fatal cases of influenza under very similar conditions, Wahl, White. and Lyall (29) obtained only negative results, while a series of similar experiments undertaken for the American Navy were also negative.

My own experience as indicated in the first part of the paper agree with the negative findings. In only one experiment out of many was the injection of filtered material followed by any abnormal symptom. In this instance a *Macacus cynomolgus* monkey, which received an inoculation of 5 c.cm. of the filtered lung juice obtained from three fatal influenza cases, became ill ten days later. It developed a running at the nose and a temperature of 103·2 F., but an uninoculated monkey in the next cage had a bad cold. The animal gradually got weaker and died 34 days after the inoculation. The post-mortem showed an accumulation of serous fluid in the pleural and pericardial sacs. The lungs were not congested and showed only a few collapsed areas. The spleen was slightly enlarged and showed a number of small yellow areas. Bacteriological and histological examinations revealed a recent septicaemia with miliary abscesses. Passage experiments were negative. This apparently was a spontaneous cold in a monkey complicated by a septicaemia.

In conclusion, it must be held that the claims to have discovered a filtrable virus of influenza are unconvincing, and that the minute bodies observed in cultures have not been differentiated with certainty from those inanimate particles present in all albuminous fluids. At the same time the human experiments are unsatisfactory in that the subjects were not isolated and the disease atypical. Similarly the infections produced in animals were atypical and the lesions indefinite. Without additional proof it is therefore impossible to accept the production of an experimental influenza by a filter-passing virus.

8. Relation of *B. influenzae* to the late Epidemic.

In the preceding chapter an attempt was made to show that the various claims so far advanced with regard to the discovery of a filter-passing virus of influenza have not been substantiated. While in view of the fact that the present research has indicated that *B. influenzae* is present in the majority of cases of influenza,

and bears a close relation to the lesions both spontaneous and experimental, it is thought advisable to correlate these findings with the results obtained by other workers. For this purpose a review of the literature is given below. At the same time one will be able to judge how far *B. influenzae* as the causative agent of epidemic influenza conforms to Koch's postulates.

Previous to the late outbreak of influenza, if one had asked what was the aetiological agent of acute influenza the answer in nine cases out of ten would have been *B. influenzae* Pfeiffer. The minority objected to Pfeiffer's claims mainly on account of the fact that this bacillus could not be demonstrated in certain epidemics which appeared to be true influenza, and that it was frequently present in other diseases. The explanation of this we shall return to later. The failure on the part of many workers satisfactorily to demonstrate this bacillus in the early part of the epidemic increased the number of dissenters. In Germany, likewise, the nature of the epidemic caused a good deal of discussion both on account of the aberrant findings of the bacillus and of the clinical features. A census of the opinion of the chief bacteriologists and others was obtained by means of telegrams without achieving any very definite result. These inconsistent findings are fully elaborated in the review on the subject of influenza in the *Medical Supplement* of 1918 (30).

Thus it was not to be wondered at that many considered that the epidemic was something other than acute influenza. But a more careful consideration of the clinical and bacteriological features of the outbreak modified this opinion considerably as time went on. Many individual workers, including the writer, went through the same period of uncertainty as to the part played by *B. influenzae*. In fact, the epidemic can be divided into two stages, a first, in which *B. influenzae* was seldom demonstrated, and a second. in which this bacillus was demonstrated with great regularity. This fact is not attributable to any alteration in the epidemic itself, but to the application of new methods for the demonstration of the bacillus of influenza.

B. influenzae Pfeiffer is by no means easy to demonstrate in the lesions and sputum of influenza cases. It is a small bacillus with no distinctive staining reactions such as those of the tubercle or diphtheria bacillus. Thus, unless present in very large numbers it is almost certain to be missed if microscopic means are alone employed. This diagnostic difficulty is further complicated by the inability of the bacillus to grow on ordinary laboratory media.

Until quite recently it was always believed that the addition of a little blood to any of the ordinary laboratory media was sufficient to obtain a growth of *B. influenzae*. This, however, is only true in a restricted sense, as the growth obtained is minimal and the largest colonies mere points on the surface of the medium. This type of medium was used early in the epidemic with most unsatisfactory results. The discovery, or rather rediscovery, that unaltered blood did not provide the best medium completely changed the aspect of affairs. Immediately following on the demonstration that the addition of a little blood altered by heating,

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or by digestion, to ordinary media enabled luxuriant growths to be obtained, the problem of the demonstration of *B. influenzae* was solved. From that time onwards careful workers reported the presence of *B. influenzae* in the majority of cases of influenza.

For reasons indicated on the previous pages the bacteriological observations made in the beginning of the epidemic on the incidence of *B. influenzae* are not of much value. We have, therefore, confined most of our remarks to those observations made at a later date. By this time the majority of bacteriologists were familiar with the use of the new selective media.

Incidence of B. influenzae.

Uncomplicated influenza. In the spring of 1918 Matthews (6) by means of his special medium found *B. influenzae* in all his cases of acute influenza (12), Eyre and Lowe (73) in 12 out of 14 sputa, Fildes, Baker and Thompson (32) in 12 out of 15 uncomplicated cases, and McIntosh (33) in an acute epidemic among nurses in 8 out of 12, and Martin in 76 per cent. (34). More recently Schorer (35) in 81 cases found the bacillus in 91·5 per cent. On the other hand, Little, Garofalo and Williams (36) failed to find *B. influenzae* in the exudates from the upper air passages, and used this as an argument against the influenzal nature of the epidemic. The negative results, however, are to be explained on the grounds that they used unsuitable media (Legumine serum agar). While the numerous negative findings among German workers—Gruber, Kolle, Benda, Schmore, Friedemann, Kruse, &c.—as reported by Friedberger and Konitzer (37) are probably due to the same cause.

Broncho-pneumonic cases (ante mortem). Although, clinically, most cases of acute influenza can be roughly grouped into two divisions, those with and those without pulmonary symptoms, a very careful examination of the chest will in the great majority of cases show some form of lung involvement, so that the above classification is quite arbitrary and really one of degree.

Among the first workers to demonstrate the frequence of *B. influenzae* were Hammond, Rolland, and Shore (4). They state that in an epidemic of purulent bronchitis in France during the winter of 1916–17 *B. influenzae* was present in a large number of the cases. In a series of 20, the bacillus was found in 18 of these by microscopic and cultural examinations. They therefore considered that *B. influenzae* was the cause of the epidemic and give the following reasons: The almost constant presence of the organism in the sputum and pus of affected bronchioles, and the fact that in some cases it occurred quite apart from the presence of any other organism. Shortly after this Abrahams, Hallows, Eyre and French (5), grew *B. influenzae* from 7 out of 8 cases of purulent bronchitis.

In the true epidemic period Eyre and Lowe isolated this bacillus in 12 out of 14 sputa (73), Fildes, Baker, and Thompson (32) in 45 out of 106 cases, McIntosh (33) in 42 out of 69, while Messerschmidt, Hundeshagen, and Scheer (38) demonstrated Pfeiffer's bacillus in 48·9 per cent. of the June–July epidemic and in 90 per

cent. of the September epidemic. Pfeiffer (39) himself states that in 217 sputa sent with the clinical diagnosis of acute influenza, the bacillus was present in 51·6 per cent. Dick and Murray (40) found it in 63·2 per cent. of their cases, Park (41) in 80 per cent., Medalia (42) in a large series of 2,279 cases in 76·8 per cent., and Schorer (35) in 93·8 per cent. of 242 cases. Thus, *B. influenzae* Pfeiffer may be taken as being present in from 50 to 90 per cent. of all cases of influenza showing pulmonary complications.

Blood. In the blood *B. influenzae* is only present on rare occasions, and then usually in association with other bacteria. Fleming (43) and Medalia found it a few times, but most workers have got uniformly negative results (Fildes, Baker and Thompson, McIntosh, and Dick and Murray). In the heart-blood of post-mortem cases Wilson and Steer (44) found *B. influenzae* 12 times. Similar findings have been recorded from time to time in empyemata, pericarditis, meningitis, &c.

Post-mortem material. In the beginning of the influenza epidemic almost the only organisms of importance which were demonstrated in the lung lesions were streptococci and pneumococci. Much time and trouble was spent without obtaining any evidence as to the presence of *B. influenzae.* The introduction of selective media, as already indicated, resulted in the demonstration of the bacillus in a large number of the cases as can be seen from the figures given below. Thus Fildes, Baker, and Thompson, Patterson, Little, and Williams (45) record its presence in almost all post-mortem material, Muir and Wilson (46) in 30 fatal cases leading them to remark that *B. influenzae* at least plays a very important part in the production of the lesions. Tytler, Janes, and Dobbin (48) in 60 out of 67, and Keegan (49) in 82 per cent. Olsen found the bacillus in 75 per cent. of the lungs of 220 post-mortems. Lister (47) examined the lungs of 56 natives who had died during the epidemic in the gold mines at Witwatersrand (South Africa) and found *B. influenzae* in 53. The writer found the bacillus in 36 out of 48 cases, and in a second series in 94 per cent. The negative findings have been recorded particularly by a number of German pathologists whose names have already been noted.

Histological examinations have shown that *B. influenzae* is found in close relationship to the pathological lesions. The bacillus is to be found in the whole of the respiratory tract right down into the smallest bronchi and alveoli of the lungs. As a rule, there is no general invasion of the tissues such as is the case with streptococci and pneumococci in fatal cases. The bacilli are usually to be found, however, in the lymphatics of the sub-mucosa, and from time to time in the heart-blood and empyema pus. The serous exudates in the neighbourhood of inflamed tracheal and bronchial glands may also contain the bacillus. (Dietrich (50), Wolbach (51) and personal observations.) *B. influenzae*, therefore, in its tendency to remain on the surface without invading the tissues, may be likened to *B. diphtheriae.*

In other diseases. B. influenzae has been demonstrated in the respiratory tract of a variety of other conditions such as measles, whooping cough, phthisis, &c., but at present the exact frequency

is difficult to estimate as the figures given by different workers vary greatly. In such conditions as measles where the highest findings have been obtained (Park (41) 90 per cent.) the differentiation from *B. pertussis*, Bordet, must complicate matters. In trachoma haemophilic bacilli indistinguishable from *B. influenzae* have been found in as high percentage as 50. Here, however, we cannot say that *B. influenzae* does not play an important rôle, as personal observations have shown that it is a not uncommon cause of acute purulent conjunctivitis. But any estimates based on patients in hospital wards, and especially during an epidemic, tend to be fallacious, owing to the rapidity with which one carrier of the bacillus can infect the remainder of the ward. The same, of course, is true with any of the microbes to be found in the respiratory tract. In the case of haemolytic streptococci Cole and MacCallum (52) found that in the measles ward the incidence was 56·5 per cent. although on admission the incidence was 11·4 per cent.

In the normal individual. The true incidence of the extent to which *B. influenzae* is normally present in the nasopharynx of healthy individuals is also difficult to estimate, as most of the figures available are based on observations made in an epidemic period. It will, therefore, be necessary to wait for some time until accurate and reliable figures can be obtained. Fildes, Baker, and Thompson examined 71 apparently healthy men and obtained 15 positive cultures—21·1 per cent. Later, Fildes examined 76 boys on entering a training establishment and found 18 positive. In February to March, 1919, he made cultures from the throats of 177 healthy men in a barracks and obtained 64 per cent. positive. In a training-school for girls, Wadsworth (53) reports that *B. influenzae* was cultured from the throats of 3 of the inmates, who numbered 461. Pritchett and Stillman (54) found that 43 per cent. of normal individuals in the personnel of a large hospital carried the bacillus. But one is hardly justified in calling any of these individuals a normal sample of the population.

Association with other bacteria. We have already drawn attention to the well-known fact that various pathogenic bacteria, in particular cocci, are present in most catarrhal conditions of the respiratory passages and to a lesser extent in the healthy state. Therefore, any statement of their mere presence or absence can not be of much value. The difficulty, however, has been to devise a simple procedure which will give some sort of idea of the actual predominence of any particular organism. For some organisms film diagnosis is very satisfactory, for others, such as *B. influenzae*, it is almost useless. On the whole plate cultivation with a rough estimation of the number of colonies gives the best all round results.

The organisms most commonly associated with *B. influenzae* are streptococci, pneumococci, staphylococci and various Gram-negative cocci (*Micrococcus catarrhalis*, *M. pharyngis siccus*, and meningococci).

It has been shown, however, that even in the same locality the predominant associating microbe has changed from time to time. At one period it may be pneumococcus, at another haemolytic streptococci and at another Gram-negative cocci. In this country

streptococci were more frequent than pneumococci, although in America the opposite seemed to be more frequent.

Thus Fildes, Baker and Thompson found haemolytic streptococci in the majority of their post-mortems, Opie, Freeman, Blake, Small, and Rivers found that its incidence varied from 4 to 14 per cent. according to the type of case. Cole and MacCallum also found haemolytic streptococci in a large number of cases in an epidemic of pneumonia, and frequently in association with *B. influenzae*. Lister (47) found pneumococci present in 42 out of 50 lungs examined.

Pneumococci were found to be present by Opie (55) and his co-workers in from 53·6 to 69·8 per cent., and by Small and Stangl (56) in 72·7 to 84·4 per cent. The writer found pneumococci in about 30 per cent. and streptococci in 30 to 37 per cent., about one-half of which were of the haemolytic variety.

Staphylococci are not so infrequent as one would imagine, in some instances they appeared to spread in epidemic form, and to have been so frequent that it was suggested (Patrick (57)) that they were of some aetiological importance in epidemics of broncho-pneumonia. The high frequency of Gram-negative cocci in certain instances has led to the expression of a similar opinion. In addition, these cocci have been shown by microscopical examination to be in close relation to the histological changes found in the bronchi and in the lungs. Fletcher (58) demonstrated the presence of meningococci in large numbers in association with *B. influenzae* in the lungs of 11 fatal influenza broncho-pneumonias.

From time to time other organisms such as the pneumo-bacillus, pleomorphic streptococci, *B. proteus*, &c., have been found in considerable numbers.

Pathogenicity of B. influenzae.

For man. Numerous attempts to demonstrate a direct pathogenic effect of *B. influenzae* for man, by the production of acute influenza by means of pure cultures of the bacillus, have so far been almost uniformly unsuccessful. At most an evanescent or fleeting pyrexia with slight catarrhal symptoms have been produced. Lister and Taylor (28) introduced living suspensions of this bacillus and of two varieties of cocci into the noses and mouths of 9 men, and only one of those who received *B. influenzae* fell ill. The authors would not, however, ascribe this illness to influenza. Rosenau (59) treated 19 men with 13 strains with negative results. Wahl, White, and Lyall (29) and McCoy were equally unsuccessful. Park (60) in a recent communication reports two such instances and a third, in which, although no symptoms were produced, the subject became a carrier of *B. influenzae*. The most reliable means, therefore, left at our disposal are indirect procedures, namely, the demonstration of immune substances in the blood of affected individuals.

The presence of specific antibodies in the sera of patients is proof that at some not very remote period the tissues have been invaded

by that particular organism. But the converse is not exactly true, as in the case of those bacteria which invade the tissues only slightly and injure by the production of toxins the antibody response to the bacterial proteid is small. However, in spite of this, *B. influenzae* invades the tissues sufficiently to give rise to specific antibodies. Positive agglutination reactions have been obtained by a number of workers, while a few have failed. Fleming (61) obtained positive results in all of his 21 cases ; Spooner, Scott, and Heath (62) got comparable results ; but Materna and Penecke (63) only got positive results in 35 per cent. of their cases.

Complement fixation tests have also given numerous positive results, particularly in the hands of Howell and Anderson (64), Kolmer (65), Rapoport (66), and Wollestein (67). My own researches confirm these findings.

For animals. The pathogenic action of *B. influenzae* upon animals has been studied by many. In general it may be said that animals can resist large doses. Even massive doses introduced into the peritoneal cavity only cause a slight inflammation. The bacteria disappear rapidly and the animal recovers.

On the other hand, liquid cultures often exhibit marked pathogenic action. The condition produced is that of septicaemia together with a profound intoxication. There is usually diarrhoea and oedema of the subcutaneous tissues. Unfortunately subcutaneous or intraperitoneal injections do not lead to any regular lung changes. Attempts made to produce these by intra-tracheal injections of liquid cultures and suspensions of the bacilli have in most instances ended in failure. Quite recently, however, Blake and Cecil (68) by means of a culture whose virulence had been raised by passage through a series of mice were able to produce in monkeys an infection of the upper respiratory tract which could be complicated by acute sinusitis, tracheo-bronchitis and broncho-pneumonia. They used first or second subcultures on blood agar or in boiled blood of the *B. influenzae* recovered from the peritoneal exudate of monkeys with *B. influenzae* peritonitis.

In their first series 12 monkeys were inoculated by swabbing the naso-pharynx with a swab dipped in the culture, or by directly dropping the liquid culture into the nose by means of a pipette (1 c.cm.). In the animals successfully inoculated there was a rise of temperature with symptoms of coryza, blinking of the eyes, rubbing of nose, &c. The infection, as a rule, lasted from 3 to 5 days, and was usually marked by a racking cough and scanty muco-purulent secretion. Complications developed in from 24-48 hours and were as follows : sinusitis of the antrum of Highmore 5, broncho-pneumonia 2. Autopsies of the two latter showed extensive haemorrhages, peribronchial areas of consolidation with exudate of leucocytes, mononuclear and epithelial cells together with an infiltration and thickening of the alveolar walls. *B. influenzae* was obtained from both lungs in pure culture. In the second series 10 monkeys were inoculated with 1-5 c.cm. of the culture intra-tracheally through the skin by means of a syringe. Of the 10 monkeys thus inoculated 2 developed tracheo-bronchitis and 7 pneumonia. Necropsies of the pneumonia monkeys showed a

widespread fatty pneumonia with extensive haemorrhages, patchy emphysema, oedema, and slight cellular infiltration. In some of the animals the type of pneumonia was rather different, in that it was much more general and there was extensive bronchiolitis. The authors consider that the pathology of the lungs in the animals referred to above is identical with that observed in influenza in man.

A very distinctive feature of these experiments was the extreme prostration which the animals showed. The extreme and often sudden prostration, one of the chief clinical features of acute influenza, is suggestive of some sudden intoxication. Little, however, had been done to confirm this idea until Julia Parker (69), working along the lines which had been followed so successfully in the case of the anaerobes of gas gangrene, demonstrated the existence of a soluble poison in young boiled blood broth cultures. We have found that for rabbits the lethal dose of the filtrates of these cultures varied as a rule from 5 to 6 c.cm. or less. In some cases death followed almost immediately, in others the animal became ill and lay in a collapsed condition, death usually following next day. In these animals a post-mortem examination revealed numerous subcutaneous haemorrhages and characteristic lung changes.

In the guinea-pig the average intravenous lethal dose is 2 or 3 c.cm. although with some cultures it was as low as 0·5 c.cm.

Perhaps the most suggestive train of symptoms were those produced in guinea-pigs, whose death occurred in four or five hours after the injection. Immediately following the injection the animal becomes collapsed, its hair stands on end, and it tends to crouch in a corner of the cage. About an hour later the temperature is found to be subnormal, there is a discharge of frothy mucus at the nose and slight diarrhoea. The pathological changes observed were often quite striking, in fact one is surprised that such extensive changes could have occurred in such a relatively short period of time. This is particularly true of those animals which die in from 24 to 48 hours. The changes are identical with those noted in the case of rabbits, only they are more intense. The lungs are as a rule voluminous and do not retract fully when the chest is opened. On the surface is to be seen slightly sunken red areas alternating with paler lung tissue. In some definite haemorrhagic areas are observed; these at times may involve a whole lobe of the lung. On cutting into the lungs blood-stained frothy mucus escapes in considerable amount. In addition these animals have an increased susceptibility to other bacteria (pneumococci, streptococci, &c.).

Microscopically the affected areas show a typical picture of broncho-pneumonia with proliferation and desquamation of the alveolar and bronchial mucous membrane, and an infiltration of leucocytes, while the bronchioles are plugged with desquamated epithelium, leucocytes and mucus. In some the lesion was distinctly haemorrhagic in character. In most there was a considerable effusion of albuminous fluid in the alveoli of the lungs.

The supra-renals are oedematous and frequently the seat of numerous haemorrhages. The kidneys show a varying amount of parenchymatous degeneration with actual necrosis of the epithe-

lium in places. The intestines are usually congested and distended with gas, and in places show subperitoneal haemorrhages.

These experimental lesions produced by the soluble toxin of *B. influenzae* cultures present a very striking resemblance to those met with in fatal cases of influenza. The exact nature of this poison is still under observation. The important point, however, is that neither the filtrates of pneumococci nor streptococci produce these extensive lung changes. (McIntosh, 70.)

Immunity.

The presence of specific immune bodies (agglutinins, precipitins, complement fixors) in the blood serum of convalescent influenza patients as evidence of an infection by *B. influenzae* has already been commented on. As further evidence of the parasitic nature of the bacillus the effects of vaccination by means of cultures of *B. influenzae* may be quoted. It might be assumed that if it is the cause of epidemic influenza then vaccination by means of the culture should give a considerable degree of protection against the disease. But it should be borne in mind that in the case of *B. influenzae* the problem is not so simple as with other infections in which the bacteria invade the tissues. It is quite probable that even with a high humoral anti-influenzal immunity the bacillus may still be able to proliferate in the mucous membrane. In fact, we have had one or two good instances of this where an individual has been vaccinated, and his serum agglutinated *B. influenzae* to a comparatively high dilution, and he has yet developed an acute catarrh, the discharge of which contained the bacillus in large numbers. Under these conditions the attacks are short and seldom last more than 24 hours, the patient feeling none of the usual influenzal prostration.

If influenza be due to an intoxication by the poison of *B. influenzae* rather than to an actual invasion of the tissues, the vaccine, to get the best results, should be made from young cultures of toxin producing strains. In this way a certain amount of active immunization against the toxin may be produced. The best protective results have been obtained by the use of such vaccines. Duval and Harris (71) have shown that about 30 per cent. of individuals inoculated with good vaccines really developed a mild influenzal attack in which all the usual symptoms of influenza were present. We have seen one or two such instances ourselves, and this is especially liable to happen if the patient is vaccinated during the incubation period. These attacks are evanescent and only of a few hours' duration.

As regards figures, perhaps the most suggestive are those obtained by Leishman (72) from Army returns.

		Rate per 1000.		
		Incidence.	Pulmonary complications.	Deaths.
Inoculated	15,624	14·1	1·6	0·12
Non-inoculated	43,520	47·3	13·3	2·25

Equally striking are those of Duval and Harris who vaccinated over 3,000 individuals with the following result:

	No. vaccinated.	Developed influenza.		Incidence of disease in	
		No.	Per cent.	vaccinated	unvaccinated.
One injection	118	29	24		
Two injections	346	28	8		
Three ,,	2608	45	1.7	3.3 %	41.6 %
Controls	866	375	41.6		

Eyre and Lowe (31) among New Zealand troops obtained the following figures:

	Inoculated.	Uninoculated.
Approx. number	16,104	5,700
Incidence	1.3 per cent.	4.1 per cent.
Mortality	0.26 per cent.	2.2 per cent.

Friend (74) reports an apparent immunity among 633 boys at a public school although influenza was present among the servants of several of the houses.

A few writers claim to have obtained unsatisfactory results; in this respect may be mentioned Wadsworth (53), and McCoy, Murray, and Teeter (75), and Meyer (76). Wadsworth reports that in a girls' training school of 461 inmates, where protective inoculation against influenza was adopted, 166 cases of influenza among the vaccinated occurred and 37 among the unvaccinated. *B. influenzae* was found on 32 occasions out of 38 among the unvaccinated cases, and on 26 out of 30 among the vaccinated.

9. SUMMARY.

The almost constant presence of *B. influenzae* in the secretions and lesions of influenza during the late epidemic is indicative of an aetiological relationship. In fact, an incidence of over 80 per cent. may be regarded as sufficiently high to fulfil Koch's first postulate, particularly in view of the difficulty of an accurate clinical diagnosis. In addition the bacillus bears a direct relationship to the lesions. The fact that the bacillus is found in other conditions and in normal individuals, at any rate during the epidemic period, does not militate against its aetiological importance, any more than the finding of pneumococci or meningococci in healthy persons detracts from their aetiological importance. That there are several serological strains of *B. influenzae* is not a serious objection as has been urged by Park and other workers. Recent work on the pathogenic anaerobes has shown that such methods of differentiation are hyperspecific, and that strains differing widely in their agglutination reactions were found to be one and the same bacillus when tested by the toxin anti-toxin method. The immune serum of one protects equally well against any of the other strains. The pathogenic nature of *B. influenzae* is further confirmed by the presence of antibodies against it in the blood serum of convalescent influenza patients.

The second postulate which concerns the vitality of the virus is fulfilled by the facility with which *B. influenzae* can be cultivated on the new selective media with great ease.

With regard to the third postulate the position is not quite so clear as the exact relationship of the experimental influenza lesions in animals to those of man is not completely established. The disease produced in animals is only brought about with difficulty, and under conditions which ensure the presence of a large amount of toxin. The bacillus alone is almost ineffective. The disease when produced is an acute inflammation of the respiratory tract with involvement of the lungs, and the lesions observed have a very close resemblance to those of the spontaneous disease in the human subject. If this relationship be accepted then all the criteria by which a bacterium should be judged as the cause of a disease have been fulfilled.

10. Conclusions.

1. The predominating micro-organism in the secretions and lesions of the late epidemic was *B. influenzae* (Pfeiffer), which could be demonstrated in over 80 per cent. of the cases.

2. Other members of the catarrhal group of bacteria (pneumococci, streptococci, Gram-negative bacteria, &c.) were much less frequent.

3. Serological examinations, in particular the complement fixation test, confirmed an infection by *B. influenzae.*

4. Epidemic influenza, as shown by the pathological lesions, is essentially an acute inflammation of the respiratory tract.

5. In the early stages the lung changes are more suggestive of a toxic action than bacterial. In the later stages the lung picture may be complicated by other microbic infections.

6. The therapeutic effect of injections of the pooled sera of influenzal convalescents even in severe cases was very encouraging.

7. *B. influenzae* is a pathogenic microbe, producing its main lethal effect by means of a soluble toxin.

8. The experimental inoculation of animals with filtered cultures of *B. influenzae* produced pathological changes which presented a close resemblance to the changes found in man.

9. Injections of *B. influenzae* vaccine can produce in susceptible individuals a typical influenzal attack of short duration.

10. No evidence was obtained in support of the view that influenza is due to a filter-passing virus.

London, *June, 1920.*

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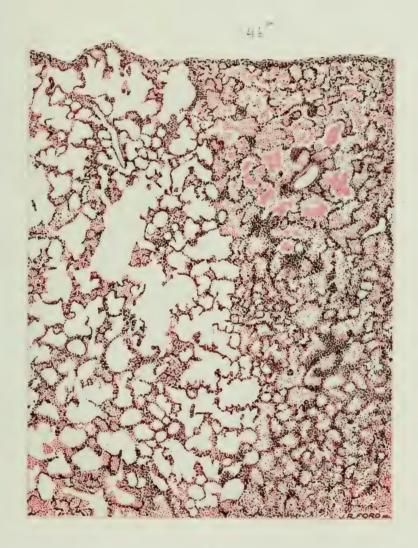
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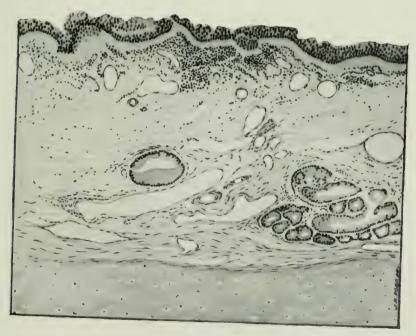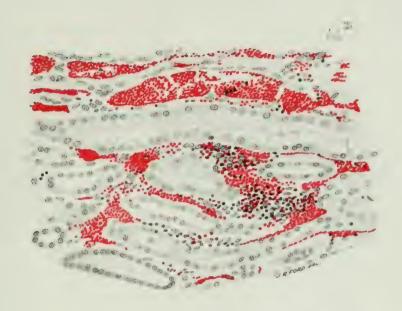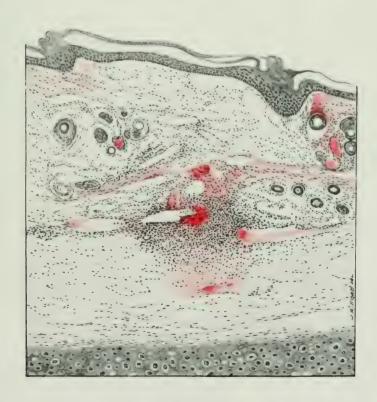
Fig. I

Fig. II

Fig. III

Fig. VI

Fig. IV.

Fig. V.

Fig. VII

MEDICAL RESEARCH COUNCIL

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CATALOGUE OF
THE NATIONAL COLLECTION
OF TYPE CULTURES

MAINTAINED AT
THE LISTER INSTITUTE OF PREVENTIVE MEDICINE
CHELSEA GARDENS, LONDON, S.W.

Medical Research Council.

National Collection of Type Cultures.

INTRODUCTION

THE Council have long had in view the formation of a National Collection of Type Cultures, from which biologists in general and bacteriologists in particular might obtain from a trustworthy source authentic strains of recognized bacteria and protozoa for use in scientific work. The need of an available supply of this kind has long been felt in many directions, and particularly in medical research work, both for the study of principles and methods in bacteriological investigations and for the systematic classification of bacteria and protozoa in their various species and strains. In the past the needs of workers in this respect have never been fully met. In this country the Lister Institute of Preventive Medicine has for many years assisted bacteriologists both at home and abroad, so far as the resources of its own private collection have permitted, but British workers have been dependent in great part upon the courtesy of scientific colleagues or upon the collections of Institutes in other countries. Before the war the collection at the Pasteur Institute in Paris, maintained by M. Binot, was very helpful to workers here. A collection of type cultures was formerly maintained on a commercial basis by Král at Prague, and this was subsequently transferred to the Serophysiological Institute of Vienna. This source of supply was never completely satisfactory, although many made use of it. In America the Museum of Natural History in New York has maintained a Culture Bureau during recent years, and it is believed that the activities of the Bureau have been of the greatest benefit to workers there, not only by the provision of authentic cultures, but also by the studies in classification made by its staff.

Early in 1920 the Council were able, by the courtesy of the Governing Body of the Lister Institute, to make arrangements to maintain a National Collection of Type Cultures at the Institute, where all the necessary facilities were provided. The scheme is under the general direction, on behalf of the Council,

of Dr. J. C. G. Ledingham, F.R.S., a member of the staff of the Lister Institute, while Dr. R. St. John-Brooks and Miss M. Rhodes have been appointed by the Council to be Curator and Assistant Curator of the Collection respectively. The Medical Research Council are greatly indebted to the Governing Body of the Lister Institute for this opportunity of establishing a central collection upon a proper footing without further delay. The present arrangement is made for a short term of years, before the end of which the future location of the Collection will be considered.

Attention has been concentrated primarily upon obtaining fully authenticated strains of pathogenic organisms, but as opportunity offers additions are also being made to the series of bacterial and protozoal strains of economic importance. Subsidiary researches are also being undertaken with a view to the discovery of economical and labour-saving methods of sub-culture. The staff of the Collection are also prepared to give help in the identification of strains received from workers at home or abroad.

It became apparent during last year that mycologists in this country felt the need of a similar collection. To some extent the Centraalbureau voor Schimmelcultures, Amsterdam (now at Baarn), has been found useful by British botanists, but it was the general opinion that a collection of fungi in this country was necessary for the co-ordination of research. As the formation of a collection of this kind was not at the time contemplated by any other institution, it was considered that the scope of the National Collection of Type Cultures should be extended in this respect. Working relations were accordingly established with the British Mycological Society, and a fully representative standing committee, of which the Curator of the National Collection is a member, has been appointed by the Society to consider and advise upon the ways in which the Collection may be made valuable to mycologists and to the study of fungi. It is proposed to collect and maintain cultures of fungi of importance in plant-pathology, medicine, veterinary science, technology, and soil biology, as well as types useful for teaching purposes and specially rare or interesting species. The mycological section of the Collection will for the present be restricted to about five hundred strains : annual lists will be published in the

Transactions of the British Mycological Society, and a set of type slides will be kept in the Botanical Department of the British Museum (Natural History) in addition to a working set in the Collection itself.

In presenting this first catalogue of strains maintained in the Collection the Council hope that workers in all spheres of microbiology will find it of value as a guide to the present resources of a collection on which they may make demands. It is also hoped that workers will in return assist the Collection by presenting new material for permanent maintenance. To the many who have already been donors the Council's grateful thanks are due, and it will continue to be the aim of the Council, and of the staff of the Collection, to maintain the fullest international reciprocity in this field.

In view of the present position of the problems involved in the classification of micro-organisms it has been thought more convenient, for the practical purposes of this Catalogue, to adopt an alphabetical rather than a taxonomic arrangement. The main list (Part I) is supplemented, however, by a subject index (Part II) giving cross-references under aetiological headings. As regards the nomenclature employed, it has been considered inadvisable to depart very widely from long-established usage: the need for international uniformity in this respect is nevertheless recognized, and it is hoped in future editions to take fuller cognizance of the labours of systematists in this and other countries.

15 BUCKINGHAM STREET,
    LONDON, W.C. 2,
       28th January 1922.

NOTE

The co-operation of bacteriologists is earnestly invited, and in return every effort will be made to supply the needs of applicants for cultures. Cultures that may be sent either for identification or for maintenance in the Collection should be accompanied by the fullest particulars as to source and date of isolation and, if possible, by clinical and epidemiological notes. It must naturally be left to the discretion of the Director to decide whether given cultures are of sufficient importance to be maintained in the Collection, but it is hoped that this will not deter workers from forwarding strains of even the commonest types of organism. These will have value in view of the necessity for maintaining an adequate representation of strains of recent origin. Studies in classification will also be aided if large series of authentic specimens of closely related species are made available for workers.

Cultures will be supplied on demand so far as possible to workers at home or abroad, and, as a rule, a small charge will be made to defray the cost of media and postage.

It is requested that all communications be addressed to THE CURATOR, NATIONAL COLLECTION OF TYPE CULTURES, LISTER INSTITUTE, CHELSEA GARDENS, LONDON, S.W. 1.

CATALOGUE OF THE NATIONAL COLLECTION OF TYPE CULTURES

PART I. ALPHABETICAL LIST OF THE ORGANISMS

WITH DETAILS OF THE STRAINS WHICH ARE MAINTAINED

Some or all of the following particulars are given, in the order named:

1. Reference Number.
2.* Other particulars of the Type, Group or Variety to which the strain belongs.
3. Name of the person or institution from whom the strain was received either directly or through some intermediate agency.
4. Name, number or letter by which the strain has been previously known. *In order to avoid confusion this is printed in italic type.*
5. Particulars of the source from which the strain was isolated. The name of the isolator, when available, and the date of isolation.
6. Other information considered likely to be useful.
7. Date on which the strain was deposited in the National Collection. This is printed at the end of the last line of each entry.

Acladium castellani Pinoy
706. Prof. Castellani. Isolated 1915. 1920
(Castellani and Chalmers, *Manual of Tropical Medicine*, 3rd Ed., 1919, pp. 1112 and 2089.)

Acrostalagmus cinnabarinus
798. *Underground.* Isolated by Dr. Graham Forbes, L.C.C., from dust of London Tube Railway, 1920. 1921

Actinobacillus
629. Royal Vet. Coll., London. *121 Ox.* Submaxillary gland of a S. American Ox. 1920

Actinomyces bovis (anaerobic type, Wolff and Israel, 1891)
783. Dr. P. Fildes, London Hosp. *Wilkinson.* Localized abscess in appendicular region and sinus. 1920
2 other strains.

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* Results of attempts to differentiate organisms of certain groups serologically are given when available. For the majority of those of the Salmonella group the Collection is indebted to Dr. Schütze, Sir Frederick Andrewes, F.R.S., and various donors. The multiplicity of names and sources attached to organisms of this group as they enter the collection has made this identification work necessary, but the results, as recorded, are, in the present state of knowledge, to be regarded only as working guides.

Actinomyces caprae
659. Lister Inst. *Lister.*   1920

Actinomyces (*Aerobic types from Man*)
600. *Horton.* Isolated by Capt. St. John Brooks, R.A.M.C., from pus containing typical actinomycotic granules from parotid abscess, Horton War Hosp., Epsom, 1919.   1920
434. Lister Inst. *Human.*   1920
    See also *Nocardia lutea* and *Nocardia tropica.*

Actinomyces (white)
390. *Soil.* Isolated by Dr. S. G. Paine, Imperial Coll. of Science, S. Kensington, 1917.   1920

Alternaria ? sp.
1007. *Ireland.* Isolated by Miss Lorrain Smith from rotting tent canvas from Ireland.   1921

Amylomyces rouxii. See *Mucor rouxii*

Amylomyces tapioca
605. A. Jörgensen's Lab., Copenhagen. *Thaysen.*   1920

Anthracoid bacillus
945. *China.* Isolated by Dr. Graham Forbes, L.C.C., from Chinese tooth-brush. Not pathogenic to guinea-pigs.   1921

Aplanobacter michiganense Erwin Smith
778. Prof. Erwin Smith, U.S.A. *Lacey.* Isolated by Miss Lacey, Imperial Coll. of Science, S. Kensington, from diseased tomato (Grand Rapids Disease).   1921

Aspergillus candidus Link
595. Centralstelle, Amsterdam. *Washington 106.*   1920

Aspergillus clavatus
978. Thom and Church, Washington, D.C., U.S.A. *Washington 107.* Type Culture.   1921

Aspergillus effusus Tiraboschi
973. Dr. F. B. Lutman, Vermont, U.S.A. *Washington 130.* (*Am. J. Botany*, 1921, **2**, 103.)   1921

Aspergillus flavus Brefeld
596. Centralstelle, Amsterdam. *Washington 108.*   1920

Aspergillus fumigatus
367. Capt. S. R. Douglas, St. Mary's Hosp. *Zoo.* White egret at Zoological Gardens, London, suffering from aspergillosis, 1916.   1920
    One other strain (No. 982).

Aspergillus luchuensis
1017. Thom and Church. *4291. 3.* Isolated by Dr. Hanzawa, Imp. University of Tokyo.   1921

Aspergillus nidulans
793. *Underground I.* Isolated by Dr. Graham Forbes, L.C.C., from dust of Tube Railway.   1921
    2 other strains (Nos. 795 and 796).

Aspergillus niger van Tieghem
603. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.* Indian cotton.   1920
    3 other strains.

Aspergillus ochraceus
979. Thom and Church. *Washington 4065. 1.*   1921
Aspergillus oryzae Ahlberg
598. Centralstelle, Amsterdam. *Washington 113.*   1920
    One other strain (No. 965).
Aspergillus parasiticus Speare
975. Thom and Church. *Mealy bug.* Isolated by Speare in Honolulu,
    1912 or earlier. Parasitic upon the mealy bug of sugar-cane
    (*Pseudococcus calceolariae* Mask). (*Am. J. Botany*, 1921, **2**,
    103.)   1921
Aspergillus repens
794. *Underground.* Isolated by Dr. Graham Forbes, L.C.C., from dust
    of Tube Railway.   1921
Aspergillus sydowi
980. Thom and Church. *Washington 3521.*   1921
Aspergillus tamari Kita
599. Thom and Church. *Washington 4235 x. l.* Soy products used in
    making salt pickles, China.   1920
Aspergillus terreus
981. Thom and Church. *Washington 144.*   1921
Aspergillus terricola var. **americana** Marchal
974. Thom and Church. *Washington.* Isolated by Scales from redland
    soil in Georgia, 1914 or earlier. (*J. Biol. Chem.*, 1914, **19**,
    459.)   1921
Aspergillus wentii Wehmer
597. Centralstelle, Amsterdam. *Washington 116.*   1920

B. abortivo-equinus (*Salmonella*, unclassified serologically)
626. Royal Vet. Coll., London. *Foal 3.* Heart blood of aborted foal,
    1917.   1920
427. Dr. Krumwiede, New York. *215.* Isolated by Dr. K. F. Meyer
    from abortion in mare.   1920
451. Prof. Murray, Iowa State Medical College. *709.* (*J. Infect. Dis.*,
    1919, **25**, 341.)   1920
766. Prof. Denys, Louvain. *Avortement cheval.* (*Compt. rend. Soc. de biol.*,
    1919, **82**, 954.)   1920
B. abortus
369. Dr. Eagleton. *1 Bang.* One of Bang's strains sent from Copen-
    hagen, 1913.   1920
624. *English strain 8.* Isolated by Capt. Edwards, R.A.V.C., Royal
    Vet. Coll., London, from stomach of foetal calf, 1919. 1920
900. Dr. K. F. Meyer. *Hog.* Isolated by Dr. Taum from liver of
    aborted hog foetus, 1920.   1921
    9 other strains from various sources.
B. aceti
612. A. Jörgensen, Copenhagen. *Thaysen.* Vinegar.   1920
B. acetoethylicum
1068. American Museum of Natural History, New York. *234. A.*
    Isolated by J. H. Northrop, Rockefeller Inst., New York.
    (*J. Biol. Chem.*, 1919, **39**, 1.)   1921
B. acidi lactici Grotenfelt, Hueppe
413. American Museum of Natural History, type strain. *131.* Faeces.
    (*J. Bact.*, 1919, **4**, 429.)   1920
    3 other strains.

B. acnes

737. *Ponsonby.* Isolated by Dr. A. F. Hayden, St. Mary's Hosp., from severe case of facial acne. 1920

    3 other strains.

B. aerofetidus Weinberg and Séguin, 1916

505. Prof. McIntosh. *208.* 1920

B. aerogenes pfeifferi. See *B. lactis aerogenes*

B. aertrycke. See *B. suipestifer*

B. anatum (*Salmonella*, type Mutton)

851. Prof. Rettger, Yale University. *Ovum W.* Isolated from ovary of duck during epizootic in Massachusetts, U.S.A. 1921

B. anthracis

108. Lister Inst. *Paddington V.* Shaving brushes, 1919. 1920

631. Royal Vet. Coll., London. *17 James.* Ear vein of cow, 1912. Avirulent. 1920

    7 other strains.

    See also *Anthracoid bacillus.*

B. asiaticus Castellani

709. Prof. Castellani. *Castellani No. 1.* 1920

    (Castellani and Chalmers, *Manual of Tropical Medicine,* 3rd Ed., 1919, pp. 944 and 1411.)

B. avisepticus

821. *Duck.* Isolated by Sir John M'Fadyean from infected duck. Duck and fowl epizootic, 1920. 1921

71. Pasteur Inst. *Fowl cholera I.* 1920

    One other strain (No. 121).

B. bifermentans Tissier and Martelly

506. Miss M. Robertson. *F. .I* 1920

    One other strain (No. 536).

B. botulinus

94. Inst. of Infectious Diseases, Berlin. *A.* 1920

95.   ditto   *B.* 1920

    Burke's Types (*J. Bact.,* 1919, **4**, 555)

750. Type A. Dr. G. S. Burke, Stanford University, Cal., U.S.A. *IX.* 1920

751. Type B. Dr. G. S. Burke. *X.* 1920

    Meyer's Types

887. Type A. Dr. K. F. Meyer, University of California, U.S.A. *38.* Crop of chicken dying of botulism, 1920. 1921

888. Type B. Dr. K. F. Meyer. *40.* Intestinal wall, human case of botulism, 1920. 1921

    2 other strains, No. 889, spinach, and No. 890, unbroken olives.

    Kirkbride's Strains

772. Type B. Dr. Mary Kirkbride, Albany, N.Y., U.S.A. *Boise.* Home-canned asparagus at Boise, Idaho, 1919. 1920

773. Type B. Dr. Kirkbride. *Nevin.* Home-made cottage cheese, 1914. 1920

B. bovisepticus

929. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *01448.* Used in preparation of sera in bovine haemorrhagic septicaemia. 1921

967. Dr. W. G. Smillie, São Paulo, Brazil. *Pasteurella Ox,* a Brazilian strain from spleen of Ox. 1921

B. bronchisepticus

452. *Dog* 71. Isolated by Dr. Ferry, Parke Davis Co., Detroit, U.S.A., from lungs of dog with distemper. (*Vet. J.*, 1912, **68**, 445.)
1920

6 other strains (Nos. 453–458) from guinea-pigs, rabbits, ferrets, monkeys, white rats and Man.

B. bulgaricus

552. *I.* Isolated by Dr. C. Lind, Copenhagen, from specimen of Yoghurt from Bulgaria, 1909.   1920

76 B. *Massol.* One of Metchnikoff's original strains, supplied by him to Prof. Eyre, Guy's Hosp., 1909.   1920
One other strain (No. 554).

Bacillus (acid-fast) from butter

524. (Butter bacillus of Rabinowitsch.) National Biological Museum, New York. *New York.*   1920

Strains of acid-fast bacilli isolated by Dr. F. Griffith from guinea-pigs inoculated with butter samples in 1912. (Rep. Local Gov. Bd. (Suppl. of Med. Officer), 1912–13, 42, 299)

337. *G.P. 330.*   1920
333. *G.P. 60.*   1920
334. *G.P. 61.*   1920

B. butylicus

619. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.* Used during the War in the manufacture of acetone and n. butyl alcohol (Weizmann, 1915).   1920

B. caratovorus

386. *Paine.* Isolated by Dr. S. G. Paine, Imperial Coll. of Science and Technology, S. Kensington, from cabbage or turnip rot. (*Ann. Applied Biol.*, 1918, **5**, 62.)   1920

B. caviae (*Salmonella* ? Type)

428. Dr. Krumwiede, New York. *146.* Isolated by Dr. Ferry from guinea-pig epizootic, Detroit, U.S.A.   1920

B. chauvoei

287. Miss M. Robertson. *203.* Isolated by Prof. McIntosh. Cattle suffering from Rauschbrand.   1920
One other strain (No. 502).

B. cloacae Jordan

408. American Museum of Natural History, type strain. *23.* Isolated by Jordan from Chicago canal drainage, 1899. (*J. Bact.*, 1919, **4**, 429.)   1920
One other strain (No. 257).

B. cochlearius Douglas, Fleming and Colebrook

535. *T.M.I.H.C.* Isolated by Miss M. Robertson from tetanus stock laboratory culture.   1920

B. coli communis

86. Lister Inst. *Escherich.* Original Escherich strain.   1920
692. Sir Alexander Houston. *Houston 2.*   1920
4 other strains.

Bacillus (coliform)

762. Prof. W. Bulloch. *J. M.* Urine in chronic cystitis, 1920.   1920

The following organisms have been grouped by Dr. Lepper in accordance with MacConkey's scheme (*J. Path. and Bact.*, 1921, **24**, 192):

Bacillus (coliform) (*continued*)

844. Group I. *Reeves.* Urine in acute cystitis, 1920. 1921
845. Group I. *A. F.* Urine in chronic cystitis, 1920. 1921
846. Group II. *Nurse S.* Urine in acute cystitis, 1920. 1921
847. Group II. *Brown.* Abscess in kidney. 1921
848. Group III. *Sherry.* Urine in acute cystitis, 1918. 1921
849. Group IV. *Phillips.* Urine, 1920. 1921

For other coliform bacilli *see* under special names.

B. columbensis Castellani

708. Prof. Castellani. *Castellani.* Isolated 1905. 1920
(*Centralbl. f. Bakt.* (*&c.*), 1914, Orig., **74**, 197 ; Castellani and Chalmers, *Manual of Tropical Medicine*, 3rd Ed., 1919, pp. 946 and 1410.)

B. communior Durham

419. American Museum of Natural History, type strain. *137.* (*J. Bact.*, 1919, **4**, 429), 1911. 1920

B. cuniculisepticus

826. *Rabbit.* Isolated by Dr. Kanai, Lister Inst., from subcutaneous abscess in a laboratory rabbit, 1920. 1921
One other strain received as *B. lepisepticum* (No. 954).

B. dendroides

927. H. G. Thornton. *Rothamsted.* Soil, Rothamsted Experimental Station, Harpenden, Herts. 1921

B. diphtheriae. See *Corynebacterium diphtheriae*

B. dysenteriae Flexner

Strains received from Sir F. W. Andrewes (M.R.C. Special Report Series, No. 42, 1919).

1. Type W. *Cable.* Isolated by Broughton-Alcock from reputed first case of dysentery, British Front, Flanders, 1914. 1920
2. Type X. *Hughes.* Carrier, University War Hospital, Southampton. 1920
3. Type V. *Oxford Flexner.* Strain used in Standards Laboratory, Oxford. 1920
727. Type V. Prof. Lentz, Berlin. *Lentz-Flexner.* 1920
4. Type WX. *Mountain 2,464.* Carrier, University War Hospital, Southampton. 1920
5. Type VZ. *Stansfield.* Carrier, University War Hospital, Southampton. 1920
6. Type Y. American Museum of Natural History, type strain *Original Hiss and Russell*, from General Russell himself. 1920
7. Type Z. *Whittington.* Carrier, University War Hospital, Southampton. 1920

Strains isolated at Lister Institute, 1918, from intestinal ulcers of monkeys naturally infected with dysentery

781. Type W. *Marice.* 1920
712. Type Y. *Paddi.* 1920
13 other strains, various types and sub-types.

B. dysenteriae Schmitz. *See B. schmitz*

B. dysenteriae Shiga

152. *Wynne.* Isolated by Dr. Ledingham, King George Hosp. Case from Gallipoli, 1915. 1920

B. dysenteriae Shiga (*continued*)

187. *Parker.* Isolated by Lt.-Col. Martin at Lemnos, 1916.   1920
    5 other strains.

B. dysenteriae Sonne type II (Thjøtta III)

268. Thjøtta, Christiania. *20.* Child with dysentery. (*J. Bact.*, 1919,
    4, 355.)   1920
    One other strain (No. 269).

B. enteritidis Gärtner

75. Pasteur Inst. *Bainbridge.* Isolated 1908, unknown source. (*J.
    Path. and Bact.*, 1909, **13**, 443.)   1920

410. Rockefeller Inst. *18.* Type strain of American Museum of
    Natural History. (*J. Bact.*, 1919, **4**, 429.)   1920

125. *Limerick.* Isolated by Prof. McWeeney from food-poisoning outbreak
    in Limerick, 1910.   1920

128. *McNee.* Isolated by Dr. McNee from blood and broncho-pneumonic
    lesions of patient who died with symptoms of acute toxaemia,
    1917.   1920

127. *Stokes.* Case of fatal enteritis, France, 1917.   1920

126. *Newcastle.* Isolated by Prof. Hutchens from milk that caused food-
    poisoning, 1910.   1920

618. Messrs. Evans, Lescher, Son & Webb, Liverpool. *Rat Virus B*
    (*Liverpool Virus*).   1920

617. Ratin Laboratory, London. *Rat Virus A* (*Ratin*).   1920

205. Lister Inst. *Danysz.*   1920

810. *Rat.* Spontaneous infection in rat (multiple pulmonary abscesses),
    Lister Inst., 1920.   1921
    5 other strains.
    See also *B. paracoli.*

B. erysipelatis suis

808. Capt. Edwards, Royal Vet. Coll., London. *Edwards.* Vegetation
    on heart valve from case of swine erysipelas, 1920.   1920

B. faecalis alcaligenes

415. American Museum of Natural History, type strain. *439.* Faeces.
    (*J. Bact.*, 1919, **4**, 429.)   1920
    One other strain (No. 655).

B. fallax Weinberg and Séguin, 1915

508. Miss M. Robertson. *Morcom.* Blood culture from fatal case of
    gas gangrene.   1920
    2 other strains.

B. fluorescens liquefaciens

950. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *Detroit.*   1921
    One other strain (No. 964).

B. fluorescens non liquefaciens

912. *Urine.* Isolated by Dr. H. Schütze, Lister Inst., from urine, 1921.
        1921

B. gallinarum Klein

416. American Museum of Natural History. *43.* (*J. Bact.*, 1919, **4**,
    429.) Probably identical with *B. sanguinarium.*   1920
    2 other strains (Nos. 987 and 988).

B. glässer. See *B. typhi suis*

B. güntheri Lehmann and Neumann

661. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.* St. Ivel cheese.
        1920

B. herbicola aureum
   610. Dr. Thaysen. *Thaysen.* Grass.   1920

B. herbicola rubrum
   609. Dr. Thaysen. *Thaysen.* Grass.   1920

B. histolyticus Weinberg and Séguin, 1916
   503. Miss M. Robertson. *Weinberg.* Isolated by Weinberg from case
           of gas gangrene.   1920

Bacillus from Hog Cholera (*Salmonella*, type Hirschfeld)
   357. Dr. Ten Broeck. *16.* (*J. Exper. M.*, 1918, **28**, 759.)   1920

B. influenzae
   293. R.A.M. Coll., Millbank. *Smellie.* Sputum of influenza patient,
         1919.   1920
   292. *Rosenheim.* Case of acute recurring catarrh, 1919.   1920
         8 other strains.

B. johne
   910. *19.* Isolated by Dr. F. W. Twort from typical case of Johne's
         disease, 1920.   1921
         One other strain (No. **911**).

B. kützingianum Hansen
   614. A. Jörgensen, Copenhagen. *Thaysen.* Vinegar.   1920

B. lactis aerogenes Escherich
   418. American Museum of Natural History, type strain. *240.* Probably
         descended from Pfeiffer's original Capsule Bacillus. (*J. Bact.*,
         1919, **4**, 429.)   1920
         One other strain (No. **243**).
         See *Leather Bacillus.*

B. lathyri
   389. *Tomato.* Isolated by Dr. S. G. Paine, Imperial Coll. of Science,
         S. Kensington, from tomatoes, 1919. (*Ann. Applied Biol.*,
         1919, **6**, 183.)   1920

Bacillus from Leprosy
         Strains received from Prof. Duval, New Orleans, U.S.A.
   509. 'Kedrowsky.' Kraus, Vienna. *Kraus.*   1920
   510. 'Rost and Williams.'   1920
   511. 'Nabarro-Bayon.'   1920
   512. 'Clegg I.'   Recovered from leprous lesions by Clegg. 1920
   513. 'Clegg II.'   ,,   ,,   ,,   ,,   ,,   ,,   1920
   514. 'Duval's Chrome.'   ,,   ,,   ,,   ,,   ,,   Duval. 1920
   515. 'Levy Chrome.' Kraus, Vienna. *Kraus.*   1920
   516. 'Brinckerhoff I.' Recovered by Brinckerhoff from leprous lesions.
                                             1920
   517. 'Brinckerhoff II.'   ,,   ,,   ,,   ,,   ,,   ,,
                                             1920
   518. '18.'   1920
   519. 'Barry.'   1920
   520. 'Reinsteiner.' .   ·1920
   521. ' Currie.'   1920
   522. 'Elly.'   1920

B. mallei
   625. Royal Veterinary College. *Minett.* Lung of horse, 1918. 1920
         One other strain (No. **120**).

B. megatherium
   654. Lister Inst. *Lister.*   1920

B. melitensis.

80. *Arkwright.* Isolated by Dr. Arkwright from blood of Malta fever patient, Malta, 1915–16. 1920

311. *Zammit. I.* Isolated by Dr. Zammit, Malta, from milk of goat suffering from undulant fever. 1920

Feusier and Meyer's Types (*J. Infect. Dis.*, 1920, **27**, 185)

893. Group I. R.A.M. Coll., Millbank. *20*, originally *Austria I.* 1921

892. Group II. Race Monaco. Inst. Pasteur d'Algérie. *8.* 1921

894. Group II. Dr. Eyre, Guy's Hosp. *27*, originally *Goat.* Goat's milk, Malta. 1921

891. Group III. Inst. Pasteur d'Algérie. *7*, originally *R. Mun. 5.* 1921
    12 other strains.

B. mesentericus

656. Lister Inst. *Lister.* 1920

Miss Jordan Lloyd's Types isolated in 1917 from Ropy Bread (see *J. Hyg.*, 1921, **19**, 380)

1023. Type A. 1921

1024. Type B. *B. I.*

1025. Type C. *C. II.*

1026. Type D. *D. II.*

1027. Type E. *E. II.*

B. mesentericus panis viscosi

962. A. Chaston Chapman, F.R.S. *Chapman.* Ropy bread. 1921

B. Morgan No. I.

235. *33 M.* Isolated by H. de R. Morgan from case of summer diarrhoea. (*Brit. M. J.*, 1906, i, 208.) 1920

417. American Museum of Natural History, type strain. *692.* Stool of infant at Providence City Hosp. 1920
    3 other strains.

B. mori

957. *Wormold.* Isolated by Dr. H. Wormold at S.E. Agricultural Coll., Wye, from mulberries, 1920. 1921

B. murisepticus

807 A. *Topley A.* Isolated from spontaneous mouse epizootic by Dr. W. W. C. Topley, Charing Cross Hosp. 1921
    One other strain (No. 807).

B. mycoides

143 A. Prof. Hewlett (1918). *Hewlett.* 1920

926. H. G. Thornton. *C. R. ii Rothamsted.* Soil, Rothamsted Experimental Station, Harpenden, Herts. 1921

B. neapolitanus Fraenkel

414. American Museum of Natural History, type strain. *126.* Urinary fistula, 1911. (*J. Bact.*, 1919, **4**, 429.) 1920

B. necrophorus

650. Royal Veterinary College, London. *Cow.* Abscess in liver of slaughter-house cow, 1920. 1920
    One other strain, (No. 651).

B. nephritidis equi Meyer, 1910. See *B. viscosum equi*

B. oedematiens Weinberg and Séguin, 1915

277. *Cossard.* Isolated by Miss M. Robertson in Weinberg's Laboratory, Paris, from fatal case of gas gangrene, 1918. 1920
    3 other strains.

B. ovisepticus

930. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *01365*. Used in preparation of sera in ovine haemorrhagic septicaemia. 1921

B. ozaenae Perez

459. Dr. Ferry. *110895*. Isolated by H. C. Ward in Parke Davis Co. Lab., Detroit, U.S.A. 1920
2 other strains (Nos. 1060 and 1061).

B. paracoli Jensen (*B. enteritidis* Gärtner)

577. Sir F. W. Andrewes. *Calf No. 1306.* Isolated by Prof. Jensen, Copenhagen, from enteritis in calves. 1920
Two other strains (Nos. 578 and 579) from calves, Copenhagen.

B. paramelitensis

(Feusier and Meyer's *B. melitensis*, Group IV)
82. Dr. Nicolle, Tunis. *Bassett-Smith*, originally *Br*. 1920
2 other strains.

B. parasporogenes McIntosh, 1917

276. Miss M. Robertson. *R. 60 XV.* Material from an outbreak of ' blackleg ' in Ireland. 1920

B. paratyphosus A Schottmüller

13. Lister Inst. *Schottmüller*. Original Schottmüller strain. 1920
133. *Haddon.* Blood, King George Hospital, London, 1915. 1920
420. American Museum of Natural History, type strain. *16.* (*J. Bact.*, 1919. **4**, 429.) 1920
4 other strains.

B. paratyphosus B Schottmüller (*Salmonella*, type Schottmüller)

15. Lister Inst. *Schottmüller-Bainbridge.* Original Schottmüller strain. 1920
14. *Tidy.* Blood, King George Hospital, London, 1915. 1920
156. Lister Inst. *Achard.* Original Achard strain. 1920
421. American Museum of Natural History, type strain. *22.* (*J. Bact.*, 1919, **4**, 429.) 1920
267. *Thjøtta.* Mucoid variety. Isolated by Thjøtta. 1920
359. *Fletcher.* Mucoid capsulated variety. Isolated by Fletcher from urine, 1917. (*Lancet*, 1918, ii, 102.) 1920
16 other strains.

B. paratyphosus C (*Salmonella*, type Hirschfeld)

90 *Para C.* Original strain isolated by Hirschfeld in Salonika. (*Lancet*, 1919, i, 296.) 1920
96. *Bagdad 31.* Isolated by MacAdam, 1918. (*J. Roy. Army Med. Corps*, 1919, **33**, 140.) 1920
99. *Bagdad 782.* Isolated by Major Gloster, I.M.S., 1917. 1920
101. *Bagdad 1251.* Isolated by Mackie and Bowen. (*J. Roy. Army Med. Corps*, 1919, **33**, 154.) 1920
309. *Postulat.* Isolated by Fry and Lundie from German prisoner of war, Rouen, 1919. (*Lancet*, 1919, ii, 51.) 1920
777. *East Africa.* Isolated by R. P. Garrow from blood in case in Portuguese East Africa. (*Lancet*, 1920, i, 1221.) 1920
10 other strains.

B. paratyphosus C Heiman (*Salmonella*, type Hirschfeld)

749. Král, Vienna. Food-poisoning in Man. (*Centralbl. f. Bakt.* (*&c.*) *Orig.* 1912, **66**, 211). 1920

B. pasteurianum Hansen

613. A. Jörgensen, Copenhagen. *Thausen.* Vinegar. 1920

B. pertussis. Bordet.
364. Prof. Hektoen through St. Mary's Hosp., London. *Hektoen.* 1920
     5 other strains.
B. pestis
144 A. *Parel.* Guinea-pig inoculated, 1920, with strains of *B. pestis*, stock organisms used for making Haffkine's prophylactic vaccine at Parel, Bombay.   1920
329 A. *Ceylon.* Isolated by Castellani in Ceylon, 1914. (*Brit. M. J.*, 1914, i, 752).   1920
330 A. *Strong.* Strong's avirulent strain used for living attenuated vaccine, Philippine Islands. (*Philippine J. Sc.*, 1907, 2, 155.)   1920
331. *24 Manchuria.* Isolated by Dr. Petrie, Manchurian epidemic, 1910–11.   1920
     6 other strains.
B. phlei
525 National Biological Museum, N.Y. *Hay.* Hay.   1920
     One other strain (No. 54).
B. pneumoniae Friedländer
204. *L.I.P.M.* Probably original Friedländer strain.   1920
B. prodigiosus
256. Lister Inst. *Lister.*   1920
B. proteus anindologenes
59. Prof. van Loghem, Amsterdam. *Elders.* Case of Indian sprue. (*Ann. de l'Inst. Past.*, 1918, 32, 295.)   1920
B. proteus mirabilis
403. University of Michigan. *Novy.* Through Prof. Rettger. (*J. Bact.*, 1919, 4, 331.)   1920
B. proteus vulgaris
65. *K. 6.* Isolated by Dr. G. H. K. Macalister from case of food-poisoning at Yeadon, Yorks., 1913.   1920
67. *X. 19.* Strain used in the Weil-Felix reaction.   1920
401. New York University. *N.Y.U.* Through Prof. Rettger. (*J. Bact.*, 1919, 4, 331.)   1920
B. proteus zenkeri
405. University of Chicago. *Chicago.* Through Prof. Rettger. 1916 (*J. Bact.*, 1919, 4, 331.)
     17 other strains of *B. proteus* of various types.
B. pseudotuberculosis rodentium
941. *Guinea-pig 3. a.* Isolated by Dr. Schütze at Lister Inst. from lesion of guinea-pig, 1921.   1921
824. Dr. David, Statens Bakt. Lab., Stockholm. *Stockholm.*   1921
     2 other strains (Nos. 70 and 251).
B. psittacosis (*Salmonella*, type Mutton)
776. Lister Inst.   1920
B. pullorum
397. *17.* Isolated by Prof. Rettger, Yale, from affected chicks, 1917. (*J. Med. Research*, 1916–17, 35, 443.)   1920
969. *Chick I.* Isolated at National Collection of Type Cultures from abscess in lung of affected chick, 1921. Material supplied by Miss Edith Knight.   1921
     6 other strains (Nos. 395, 396, 409, 424, 970, and 971).
B. putrificus coli
260. Lister Inst. *L.I.P.M.*   1920

B. pyocyaneus
    42 A. Prof. Bulloch. *Bulloch.* Case of cystitis, London Hosp., 1920.
                                                                 1920
    150 B. Dr. Fildes, London Hosp. *Fildes.* Case of gas gangrene of leg,
        1920.   1920
    254. Lister Inst. *Goat.* Stomach contents of goat, 1913.   1920

B. sanguinarium
    398. Prof. Theobald Smith. *Harvard.* Isolated 1914.   1920
           2 other strains (Nos. 399 and 423).
           See also *B. gallinarum.*

B. schmitz
    306. Sir F. W. Andrewes. *Hawkins.* Isolated by Dr. W. Fletcher from
           dysentery patient, University War Hosp., Southampton, 1918.
                                                    1920

Bacillus of Schweinpest (*Salmonella*, type Mutton)
    748. Král, Vienna. *Schnürer.* Swine fever.   1920

B. smegmatis
    523. National Biological Museum, New York. *New York.*   1920
           One other strain (No. 53).

B. solanisaprus
    385. Museum of Natural History, Washington, D.C. *Washington.* (*J.*
           Agricult. Sc., 1917, **8**, 480.)   1920

B. sphenoides Douglas, Fleming and Colebrook
    507. Miss M. Robertson. *Tholby.*   1920

B. sporogenes Metchnikoff
    533. *Bellette.* Isolated by Miss M. Robertson from a case of severe local
             gangrene, 1918.   1920
           3 other strains.

B. subtilis
    85. Lister Inst. *Hay.* Hay, 1916.   1920
           2 other strains (Nos. 1049 and 1050).

B. suipestifer (*Salmonella*, type Arkansas)
    179. *Arkansas.* (Old Lister Inst. strain.) Hog cholera. (Schütze, *Lancet*,
           1920, i, 93.)   1920

B. suipestifer (*Salmonella*, type Binns)
    73. *Binns.* Isolated by Dr. McNee from a case of food-poisoning in
           Man, France, 1917.   1920
    175. *Arkwright 1.* Isolated by Dr. Arkwright in Malta.   1920

B. suipestifer Uhlenhuth (*Salmonella*, type Hirschfeld)
    352. Reichsgesundheitsamt, Berlin.   1920
           5 other strains of porcine origin (Nos. 347, 349, 350, 351, 356).

B. suipestifer (*Salmonella*, type G)
    91. *G.* Isolated at Lister Inst. from mesenteric gland of a monkey that
           died in the course of a dietetic experiment, 1917.   1920

B. suipestifer (*Salmonella*, type Mutton)
    74. *Mutton.* Food-poisoning in Man, Newcastle, 1911.   1920
    115. *Woodhead* Isolated by Lieut.-Col. Martin from blood in case of
           food-poisoning in France. (*J. Roy. Army Med. Corps*, 1919,
           33, 37.)   1920
           4 other strains from same outbreak of food-poisoning (Nos. 116,
           117, 118, 119).

B. suipestifer (*Salmonella*, type Mutton) (*continued*)

178. *MacConkey*. Isolated by Dr. MacConkey from cooked rabbit, consumption of which caused fatal infection in child. (*J. Hyg.*, 1905, **6**, 570). 1920

32. *Calf 32. Blood*. Isolated by Major Gloster. I.M.S., from blood of calf, epizootic of enteritis in calves, Amara, Mesopotamia, 1918. 1920

2 other strains from this epizootic (Nos. 31 and 33).

106. *Skunk*. Isolated by Dr. McGowan from spleen of skunk, epizootic in skunk farm in north of England.

959. *G.P.K. 1*. Epizootic among guinea-pigs at Lister Inst. 1920.
1921

B. suipestifer (*Salmonella*, type Newport)

129. *Newport*. Isolated from case of fatal food-poisoning in Man, 1915. (Schütze, *Lancet*, 1919, i, 93.) 1920

726. *Liston 197*. Isolated by Major Glen Liston, I.M.S., from stool of 'Para B' carrier, Richmond, 1917. Typed by Schütze, Oct. 1921. 1920

B. suipestifer (*Salmonella*, type Reading)

72. *Reading*. Isolated by Dr. Schütze from water-supply, Reading, 1916.
1920

B. suipestifer (*Salmonella*, type Stanley)

92. *Stanley*. Isolated by Prof. Hutchens from case of food-poisoning in Man, 1917. 1920

B. suis (*Salmonella*, type Hirschfeld)

426. Dr. Krumwiede, New York. *131*. 1920

B. suis (*Salmonella*, type Mutton)

425. Dr. Krumwiede, New York. *112*. Source unknown. 1920

B. suisepticus

931. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *01270*. Used in preparation of sera in porcine haemorrhagic septicaemia
1921

Bacillus of Swine typhus (*Salmonella*, type Mutton)

355. *V.* Isolated by Dr. Ten Broeck from pig inoculated with filtered emulsion of viscera of pig dead of hog cholera virus, 1918. (*J. Exper. M.*, 1918, **28**, 759.) 1920

354. *I.* Isolated by Dr. Ten Broeck from pig fed on viscera of spontaneous case of hog cholera, 1917. (*J. Exper. M.*, 1918, **28**, 759.) 1920

B. tertius Henry, 1917

336. Miss M. Robertson. *P. 7. IX.* Case of gas gangrene, 1915. 1920
2 other strains.

B. tetani

280. Miss M. Robertson. *T. 3. V.* Tetanus patient, 1917. 1920

Tulloch's Types (*Proc. Roy. Soc.*, 1919, B. **90**, 145)

279. Type I. Stock culture of unknown origin, purified by Miss Robertson. *U.S.A. II.* 1920

540. Type II. Miss Robertson. *T. 67.* Tetanus patient, 1917. 1920

539. Type III. Miss Robertson. *R. 220. E.* Tetanus patient, 1917.
1920

B. tetanomorphus

500. Miss M. Robertson. *146 T.B. I.* Septic wound which also harboured a toxic strain of *B. tetani.* 1920
2 other strains.

Bacillus from trout

145. *Fish epizootic.* Isolated by Dr. Arkwright, Lister Inst., from trout found dying in River Chess. 1920

B. tuberculosis

Amphibian Strain

946. (Tortoise tubercle, Friedmann's bacillus.) Col. Perry, R.A.M. Coll.. Millbank. Obtained in Prague by Col. Russell, U.S. Medical Service, 1921. 1921

Avian Strains

51. Dr. A. Stanley Griffith. *Z. 8.* Avian virus. Liver of black-winged grackle (*Graculipica melanoptera*) from Zoological Gardens, London, 1915. 1920

224 A. Dr. Louis Cobbett, Cambridge. *Cobbett.* Avian virus. 1920

919. *Bang-Nathan-Raw.* Bang's original strain. Avian virus, attenuated. Received from Bang by Dr. Nathan Raw, M.P., 1904. 1921

Bovine Strains

46. Dr. A. Stanley Griffith. *No. 1.* Bovine virus (Dysgonic Class I). Isolated directly from tubercular pharyngeal gland of a cow. 1914. 1920

47. Dr. A. Stanley Griffith. *No. 4.* Bovine virus (Class II). Perlsucht growths of a bovine, 1914. 1920

49. Dr. A. Stanley Griffith. *H. 127.* Bovine virus, attenuated. Generalized lupus, 1912. 1920

918. *Calmette-Nathan-Raw.* Calmette's original strain. Bovine virus, attenuated. Received from Calmette by Dr. Nathan Raw, M.P., 1904. 1921

Human Strains

48. Dr. A. Stanley Griffith. *Lyons.* Human virus (Eugonic). Sputum of child, 1918. 1920

52. Dr. A. Stanley Griffith. *C. G. 116.* Human virus (Dysgonic). Pus aspirated from cervical gland of boy, 1915. 1920

50. Dr. A. Stanley Griffith. *H. 151 (6).* Human virus (Eugonic), attenuated. Generalized intractable lupus, 1919. 1920

917. *Koch-Nathan-Raw.* Koch's original strain. Human virus, attenuated. Received from Koch by Dr. Nathan Raw, M.P., 1904. 1921

914. Arloing-Courmont. *Homogène.* Prof. Nègre, Pasteur Inst., Paris. 1921

B. typhi exanthematici Plotz

787. Dr. Bernstein, Mount Sinai Hosp., New York, U.S.A. *212.* 1920

B. typhi suis Glässer (*Salmonella*, type Hirschfeld)

348. Reichsgesundheitsamt, Berlin. *Poppe.* 1920

B. typhosus

163. King George Hosp. *Howard.* Type strain. Isolated, 1916. 1920

786. *Lister.* Maintained specially for use in testing disinfectants. 1920

160. *Rawlings.* Employed in Britain and America for preparation of typhoid vaccine. 1920

18 other strains isolated from various sources (blood, faeces, and urine of cases and chronic carriers).

B. vesicatorium

1010. Dr. S. G. Paine. *Pretoria.* Isolated by Miss E. M. Doidge, Lab. of Plant Pathology, Pretoria, from South African tomato canker, 1920. (*Ann. Applied Biol.*, 1921, **7**, 407.) 1921

B. violaceus
680 A. Sir Alexander Houston, Metropolitan Water Board, London. Old
laboratory strain.   1920
One other strain (No. 827).

B. viscosum equi Adsersen, 1916 ; Magnusson, 1917
932. Dr. H. Magnusson, Malmö, Sweden. *Magnusson.* Foal with
polyarthritis and embolic nephritis. (*J. Comp. Path. and
Therap.*, 1919, **32**, 143.)   1921

B. voldagsen Dammann (*Salmonella*, type Hirschfeld)
346. Reichsgesundheitsamt, Berlin.   1920

B. voldagsen Wegener (*Salmonella*, type Hirschfeld)
747. Král, Vienna. Food-poisoning in Man. (*Ztschr. f. Hyg. u. Infek-
tionskrankh.*, 1913, **73**, 65.)   1920

B. volutans
620 Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.*   1920

B. welchii Migula 1900
273. *S. R. 9.* Isolated by Miss M. Robertson, Lister Inst., from fatal case
of gas gangrene, 1914.   1920
5 other strains.

Bacterium from vinegar
615. Dr. A. Thaysen. *Thayson.* From vinegar factory in Copenhagen.
1920

Bacterium ' X '
972. Prof. Ling, F.I.C. *Adrian Brown.* Recovered from Prof.
Adrian Brown's stock culture. Closely resembles *Saccharo-
bacillus pastorianus* van Laer. (*J. Inst. Brewing*, 1910, **16**,
641.)   1921

Blastomyces
271. Col. Cummins. *Pink.* Blood, chronic blastomycosis, Military
Hosp., Millbank, 1919.   1920
272. Col. Cummins. *White.* Urine in above case.   1920

Botrytis ? sp.
1008. *Canvas.* Isolated by Miss Lorrain Smith from rotting tent canvas.
1920

Brucella abortus Feusier and Meyer. See *B. abortus*

Brucella melitensis. See *B. melitensis*

Butter bacillus. See *Bacilli from butter*

Carlsberg Unterhefe I. See *Saccharomyces carlsbergensis*

Carlsberg Unterhefe II. See *S. monacensis*

Citromyces B Wehmer
606. A Jörgensen, Copenhagen. *Thaysen.*   1920

Coccidiodes immitis Rixford and Gilchrist, 1896
883. *3.* Isolated by Dr. K. F. Meyer, University of California, from case
of San Joaquin Valley disease or coccidiodal granuloma,
1915.   1921
884. *1.* Source as in No. 883.   1920

Coliform organisms. See *Bacillus (coliform)*

Colpidium colpoda
25 A. *Peters.* Isolated by R. A. Peters, Biochemical Lab., Cambridge,
from single cell.   1921

Corynebacterium coryzae segmentosum

934. Sir F. W. Andrewes. *Graham.* Case of nasal catarrh, 1920.   1921

Corynebacterium diphtheriae

Strains isolated from Man

380. Lister Inst., Elstree.   *Park's No. 8 (Elstree 18/79),* used in manu-
facture of diphtheria antitoxin.   ·   ·   ·   **1920**

321. Lister Inst.   *Herne.*   Healthy carrier, 1920.   Virulent.   **1920**

322. *Gentry.*   Source as in No. 321.   Non-virulent.   **1920**
9 other strains from Man.

Strains isolated from Horses

853. Dr. Petrie, Elstree.   *Horse G.*   Isolated prior to June 1918 by
Capt. Minett, R.A.V.C., from pus from suspected case of
ulcerative lymphangitis. (*J. Comp. Path. and Therap.,*
1920, **33,** 267.)   **1920**
6 other strains (Nos. 854–859) isolated by Minett from equine
lesions.

Gordon Bell's Types

Received from *Major Gordon Bell, R.A.M. College, Millbank*

1051. Group   I.   *Park 8.*   1921

1054. Group   II.   *B. W. 66.*

1057. Group III.   *B. W. 25.*
6 other strains.

Corynebacterium flavidum

764. Pasteur Inst., Paris.   *Minett.*   **1920**

Corynebacterium hofmanni

231. Lister Inst. *2.*   **1920**
3 other strains.

Corynebacterium lipolyticum

623. Rockefeller Inst.   *Rockefeller.*   Cow's milk.   **1920**

Corynebacterium pseudotuberculosis Preisz-Nocard

621. Capt. Minett, R.A.V.C.   *Watson.*   Isolated by Capt. Watson,
R.A.V.C., from horse suffering from ulcerative lymphangitis
in France, 1918.   **1920**
7 other strains (Nos. 1033–1038.)

Corynebacterium pseudotuberculosis murium Kutscher

949. Dr. W. W. C. Topley, Charing Cross Hosp.   *Mouse.*   Mouse lesion.
Pathogenic to mice.   1921

Corynebacterium pyogenes

768. Prof. Theobald Smith.   *III.*   Pneumonic lungs of calf.   1921
3 other strains (Nos. 769, 770, 771).

Corynebacterium xerosis

1041. Wellcome Research Laboratory, Brockwell Hall.   *CD 154.*   Iso-
lated from contact case of diphtheria, 1921.   1921
One other strain (1042).

Cryptococcus farcinosus

767. Prof. Nègre, Pasteur Inst., Paris.   *Rivolta.*   Cause of epizootic
lymphangitis in horses.   **1920**

Debaryomyces globosus

477. Dr. A. Klöcker, Carlsberg Lab.   *Carlsberg.*   **1920**

Diphtheroid

754. Dr. Wood, Weston-super-Mare.   *Cat.*   Cat.   **1920**
A collection of strains of diphtheroid organisms isolated from various

lesions in Man—urethra, &c., blood, wounds, mastoid disease, &c.—is maintained.   They have not been fully identified.
            See also *Corynebacterium.*

Diplococcus
    407. Dr. Ruth Tunnicliff.   *Measles.*   Blood of measles patient, 1907.
            (*J. Am. M. Ass.*, 1917, **68**, 1028.)   1921

Diplodiella
    1009. *France.*   Isolated by Miss Lorrain Smith from rotting tent canvas
            from France.   1921

Distemper bacillus
    105. *Pig 25.*   Isolated by Dr. McGowan from pig epizootic, 1919.
                                                                             1920

' El Tor' Vibrio.   See *Vibrio El Tor.*

Emmentaler Coccus
    555. Dr. C. Lind, Copenhagen.   *Lind.*   An acidifying and peptonizing
            coccus isolated from Emmentaler cheese from Switzerland.
                                                                             1920
Endodermophyton indicum Castellani
    703. Prof. Castellani.   Isolated 1911.   1920
            (Castellani and Chalmers, *Manual of Tropical Medicine*, 3rd
            Ed., 1919, pp. 1020 and 2059.)

Enterococcus.   See *Streptococcus (faecal)*

Epidermophyton rubrum Castellani
    702. Prof. Castellani.   Isolated 1915.   1915
            (Castellani and Chalmers.   *Manual of Tropical Medicine*, 3rd
            Ed., 1919, p. 1016.)

Eurotium nidulans.   See *Aspergillus nidulans*
Eurotium repens.   See *Aspergillus repens*

Faecal streptococci.   See *Streptococcus (faecal)*
Frohberg yeast.   See *Yeast (Frohberg)*

Fumago ? sp.
    968. Cause of black and dark green spots on leather.   Isolated by R. Leslie
            Collett, F.I.C., British Leather Research Ass., 1921.   1921
Fumago vagans
    986. *South Kensington.*   Isolated by R. Leslie Collett, F.I.C., from
            sooty deposit on bark from Herbarium, Natural History
            Museum, South Kensington, 1921.   Specimen had been
            conserved for 28 years.   1921

Gonococcus
    361. *St. Mary's.*   Isolated by Dr. Hayden, St. Mary's Hosp., from
            urethral discharge.   1920
            7 other strains.

Hansenia apiculata Rees.
    817. Prof. Harden, Lister Inst.   *Harden.*   1921
Hansenia apiculata Schmitz
    816. Prof. Harden.   *Harden.*   1921
Hanseniaspora valbyensis
    478. Isolated from soil, Valby, Copenhagen, by Dr. A. Klöcker, Carlsberg
            Lab.   1920

Hemispora rugosa

705. Prof. Castellani. Isolated 1910.   1920
(Castellani and Chalmers, *Manual of Tropical Medicine*, 3rd
Ed., 1919, p. 1108.)

Kefir Yeast. See *Yeast* (*Kefir*)

Koch-Weeks' Bacillus

989. Isolated by Mr. S. H. Browning, Roy. Lond. Ophthalmic Hosp., from
typical case of conjunctivitis, 1921.   1921
Another strain (No. 977).

Lactobacillus pentoaceticus Fred, Peterson and Davenport

947. *118-8.* Isolated by E. B. Fred, Dept. of Agricultural Botany and
Agricultural Chemistry, University of Wisconsin, U.S.A. Used
in the production of acetic acid from pentoses (xylose, &c.).
(*J. Biol. Chem.*, 1919, **39**, 347, and 1920, **42**, 175.)   1921

' Leather Bacillus '

672. *Houston.* Isolated by Sir Alexander Houston from leather washer of
water tap. (*12th Research Report, Met. Water Bd.*, 1916.)
Closely related to *B. lactis aerogenes*   1920

Leishmania donovani

861. London School of Tropical Medicine. *Ranger Ali.* Spleen
puncture, case of kala-azar, 1920.   1921

Leishmania tropica

11 B. Dr. Row, Bombay. *Patton.* Typical Oriental sore, 1914.   1921

Leptospira icterohaemorrhagiae

636 A. Prof. Stokes. *America 2.*   1921

Leptospira icteroides Noguchi

634 A. Prof. Adrian Stokes, T.C.D. *Merida.*   1921
635 A. Prof. A. Stokes. *Areas.*   1921

Leptothrix

925. *1 Gifford.* Isolated by Dr. H. Gifford, Omaha, Neb., U.S.A.,
from conjunctival sac in conjunctivitis. (*J. Infect. Dis.*, 1920,
27, 296.)   1921

Logos Yeast. See *Yeast* (*Logos*)

Marpmann's Bacillus

335. *Marpmann.* Acid-fast bacillus, isolated by Marpmann from urine.
Old culture from Bayon's stock, 1912.   1920

Mather's Coccus

435. Prof. Jordan, Chicago. (*J. Infect. Dis.*, 1912, **25**, 28.)   1920

Meningococcus

668. Type I. Major Gordon Bell, R.A.M. College, Millbank. *Littledale.*
Cerebro-spinal fluid.   1920
669. Type II. Major Gordon Bell. *Morgan.* Cerebro-spinal fluid. 1920
670. Type III. Major Gordon Bell. *Jackson.* Cerebro-spinal fluid.
                                                            1920
671. Type IV. Major Gordon Bell. *Hicks.* Cerebro-spinal fluid. 1920
9 other strains — Nos. 213, 214, 1013 and 1032 (Type I),
Nos. 215 and 217 (Type II), Nos. 218 and 219 (Type III),
No. 220 (Type IV).

Micrococcus catarrhalis
345. *Gordon.* Isolated by Dr. M. H. Gordon from broncho-pneumonic
     sputum, 1920.   1920
     One other strain (No. 225).

Micrococcus flavus
664. Group I. *Ling.* Isolated by Major Gordon Bell from normal naso-
     pharynx, 1920.   1920
665. Group II. *Heller.* Isolated by Major Gordon Bell from normal
     nasopharynx.   1920

Micrococcus pharyngis siccus
666. *Lewis.* Isolated by Major Gordon Bell from normal nasopharynx,
     1920.   1920

Micrococcus tetragenus
951. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *0584.*   1921

Möller's ' Mist ' Bacilli
526. National Biological Museum, New York.   1920
527. No. 2. National Biological Museum, New York.   1920

Monilia albicans
714. *Craik.* Isolated by Dr. Craik, Ealing, from mouth of child suffering
     from thrush, 1920.   1920
(For genus *Monilia* see Castellani and Chalmers, *Manual of Tropical
     Medicine,* 3rd Ed., 1919, p. 1079 et seq.)

Monilia candida
922. A. Chaston Chapman, F.R.S. *Chapman.*   1921

Monilia kruzei
698. Prof. Castellani. Isolated, 1909.   1920

Monilia macedoniensis
697. Prof. Castellani. Isolated 1917.   1920

Monilia pinoyi
707. Prof. Castellani. Isolated 1910.   1920

Monilia ? psilosis
1065. Dr. J. T. Duncan, London School of Trop. Med. *Panton.* Iso-
     lated from faeces of acute sprue case at Endsleigh Gardens
     Hospital. Agrees with description of *Parasaccharomyces
     ashfordi,* Anderson.   1921
     4 other strains.

Monilia tropicalis
696. Prof. Castellani. Isolated 1909.   1920

Monilia zeylanica
699. Prof. Castellani. Isolated 1909.   1920

Mucor mucedo
809. Prof. Harden. *Bread.* Mouldy bread at Lister Inst.   1921
     One other strain (No. 924).

Mucor rouxii
921. A. Chaston Chapman, F.R.S. *Chapman.* Found in Chinese yeast.
                                                                1921

Mucor stolonifer. See *Rhizopus nigricans*

Mycoderma cerevisiae
819. Prof. Harden, Lister Inst. *Harden.*   1921

Nocardia dessenviller

800. *94 Underground.* Isolated by Dr. Graham Forbes, L.C.C., from dust of London Tube Railway, 1920.   1920
6 other strains.

Nocardia indica

1040. *Mycetoma.* Isolated by Col. Cornwall, I.M.S., Pasteur Inst. for S. India, from material from sinus in leg of mycetoma patient, 1921.   1921

1070. *Madura Foot.* Isolated by Dr. J. H. Harvey Pirie, South African Inst. of Medical Research, Johannesburg, from M'Sutu native suffering from Madura foot, 1921. (*Med. J. of S. Africa,* 1921, **17**, 6.)   1921

Nocardia lutea

576. Sir F. W. Andrewes. *Khartum.* Isolated by Dr. Christopherson. Eye disease, Khartum, 1918.   1920

Oidium asteroides

700. Prof. Castellani. Isolated 1914.   1920
(For genus *Oidium* see Castellani and Chalmers, *Manual of Tropical Medicine,* 3rd Ed., 1919, p. 1093.)

Oidium lactis

923. A. Chaston Chapman, F.R.S. *Chapman.*   1921

Oidium rotundatum

701. Prof. Castellani. Isolated 1911.   1920

Parasaccharomyces ashfordi Anderson

1062. Dr. J. T. Duncan, London School of Trop. Med. Isolated from a sprue patient by Dr. B. K. Ashford in Porto Rico. (Anderson, *J. Inf. Dis.,* 1917, **21**, 341.)   1921

Pasteurella

948. *Mouse.* Isolated by Dr. W. W. C. Topley, Charing Cross Hosp., from lesions of mouse, mouse epizootic.   1921

966. Dr. W. G. Smillie, São Paulo, Brazil. *Rat.* Guinea-pig inoculated with kidney of infected rat. (*J. Infect. Dis.,* 1920, **27**, 378.)   1920
See also *B. avisepticus, B. bovisepticus, B. ovisepticus, B. suisepticus, B. cuniculisepticus.*

Penicillium album camemberti

601. Liebefeld, Berne, Switzerland. *Thaysen.*   1920

Penicillium avellaneum

984. Thom and Church, Washington, D.C., U.S.A. *Washington 4010. 5.*   1921

Penicillium brevicaule Saccardo

580. Thom and Church. *Washington 2.* Cheese.   1920
581. (Var. *album* Thom.) Thom and Church. Camembert cheese.   1920

Penicillium camemberti Thom

582. Thom and Church. *Washington 5.* Found in Camembert cheese.   1920
583. (Var. *rogeri.*) Thom and Church. Found in Camembert, Brie, and Neufchâtel cheeses.   1920

Penicillium candidum

602. Liebefeld, Berne, Switzerland. *Thaysen.*   1920

Penicillium chrysogenum Thom
589. Thom and Church.   *Washington 26.*   1920
Penicillium divaricatum Thom
590. Thom and Church.   *Washington 34.*   Mucilage bottle.   1920
Penicillium duclauxi Delacroix
587. Thom and Church.   *Washington 20.*   1920
Penicillium expansum Link
593. Thom and Church.   *Washington 4189.*   Apple with coremiform
        rot.   1920
        One other strain (No. 976).
Penicillium lilacinum Thom
584. Thom and Church.   *Washington 8.*   Common in soil.   1920
Penicillium luteum Zukal
585. Thom and Church.   *Washington 11.*   Common in soil.   1920
Penicillium oxalicum
983. Thom and Church.   *Washington 103.*   Type culture.   1921
Penicillium pinophilum Hedgcock
1151. Thom and Church.   *Washington.*   Type strain, from pine wood.
                                                                   1921
Penicillium roqueforti Thom
588. Thom and Church.   *Washington 18.*   Characteristic of Roquefort
        cheese.   1920
Penicillium rugulosum Thom
592. Thom and Church.   *Washington 46.*   Isolated at Storrs, Conn.,
        U.S.A.   1920
Penicillium spinulosum Thom
591. Thom and Church.   *Washington 45.*   From a laboratory culture,
        Hanover, Germany.   1920
Phycomyces nitens
1011. King's College for Women, Camden Hill Rd., W.   ·   1921
Pichia alcoholophila
481. Dr. A. Klöcker, Carlsberg Lab.   *Carlsberg.*   From soil, Denmark.
                                                                   1920
Pichia calliphorae Klöcker
483. Dr. A. Klöcker.   *Carlsberg.*   From a fly (*Calliphora erythrocephala*)
        found in a Carlsberg garden, 1900.   (*Compt. rend. des trav. du
        Lab. Carlsberg*, 1913, **10**, 216.)   1920
Pichia farinosa Lindner-Hansen
901. A. Chaston Chapman, F.R.S.   *Chapman.*   The species was dis-
        covered in Danzig 'Jopen' beer, and has also been found
        by F. Sato in Japanese soya sauce.   1921
Pichia membranaefaciens Hansen
479. Dr. A. Klöcker.   1920
Pichia polymorpha Klöcker
480. Dr. A. Klöcker.   *Carlsberg.*   From soil, Denmark.   (*Compt. rend.
        des trav. du Lab. Carlsberg*, 1913, **10**, 215.)   1920
Pichia suaveolens Klöcker
482. Dr. A. Klöcker.   *Carlsberg.*   From soil, Denmark, 1904.   (*Compt.
        rend. des. trav. du Lab. Carlsberg*, 1913, **10**, 211.)   1920
Pneumococcus
339. Type I.   Rockefeller Inst.   *F. 1692.*   Blood, lobar pneumonia.
                                                                   1920

Pneumococcus (*continued*)

222 A. Type I.   Prof. Glynn, Liverpool.   *95*.   1920
340. Type II.   Rockefeller Inst.   *II. 75*.   Blood, lobar pneumonia.
                                                                                     1920
341. Type II.   Rockefeller Inst.   *F. 208. 2*.   Sputum, lobar pneumonia.
                                                                                     1920
342. Type II a.   Rockefeller Inst.   *Jn. 98*.   Maxillary antrum pus,
          1915.   1920
343. Type II b.   Rockefeller Inst.   *W. 67*.   Lung puncture, primary
          pneumonia (child), 1915.   1920
344. Type III.   Rockefeller Inst.   *A. 66. 31*.   Sputum, lobar pneumonia,
          1913.   1920
223. Type III.   Rockefeller Inst.   *R. III*.   1920
996. Type IV.   Dr. F. Griffith.   *B. 32*.   A typical pneumococcus strain
          isolated from sputum through mouse.   Pneumonia.   1921
              4 other strains, Type I; 2 others, Type II; another, Type III;
              3 others, Type IV.
739. *Guinea-pig*.   Isolated by Dr. Schütze from heart blood of guinea-pig
          dying at Lister Inst., 1920.   1920

Polyspora lini

1004. R. Leslie Collett, F.I.C.   *6004*.   Isolated from diseased flax by
          Dr. Pethybridge, Imp. Coll. of Science, Dublin.   1921

Pseudomonas barkeri

393. Dr. S. G. Paine.   *Barker*.   Isolated by Barker from infection with
          Barker's pear blossom blight.   (*Ann. Applied Biol.*, 1918, **5**,
          62.)   1920

Pseudomonas campestris

388. *Paine*.   Isolated by Dr. S. G. Paine, Imperial Coll. of Science,
          S. Kensington, from a cauliflower infected with black rot, 1918.
          (*Ann. Applied Biol.*, 1918, **5**, 62.)   1920

Pseudomonas (denitrifying)

933. *G. I. A. Rothamsted*.   Isolated by H. G. Thornton from Barnfield
          soil, Rothamsted, 1921.   Resembles *Bacillus New Jersey* (J. G.
          Lipman, *N. J. Agr. Stat. Rept.*, 1902, p. 183).   1921

Pseudomonas hyacinthi

387. *Paine*.   Isolated by Dr. S. G. Paine from a hyacinth bulb infected
          with Wakker's disease, 1915.   (*Ann. Applied Biol.*, 1918, **5**,
          62.)   1920

Pseudomonas phaseoli

958. *Lacey*.   Isolated by Miss M. S. Lacey from beans, 1920.   1921

Pseudomonas proteomaculans

394. *Kew*.   Isolated by Dr. S. G. Paine from diseased leaves of *Protea
          cyranoides*, Kew Gardens.   (*Ann. Applied Biol.*, 1919, **6**, 27.)
                                                                                     1920

Pseudomonas radicicola

928. H. G. Thornton, Rothamsted Experimental Station, Harpenden.   *Soy
          Bean*.   Nodule of soy bean, 1920.   1921

Pseudomonas tolaasi

392. *Mushroom*.   Isolated by Dr. S. G. Paine from mushroom infected
          with brown-spot disease, 1916.   (*Ann. Applied Biol.*, 1919,
          5, 206.)   1920

Pseudosaccharomyces (Apiculate Yeasts)
          (*Compt. rend. de trav. du Lab. Carlsberg*, 1913, **10**, 285.)

Pseudosaccharomyces africanus
499. Dr. A. Klöcker. *Akbari 12.* Soil, Akbari, Algeria.   1920

Pseudosaccharomyces antillarum
490. Dr. A. Klöcker. *St. Thomas 208.* Soil, St. Thomas, W.I.   1920

Pseudosaccharomyces apiculatus Reess
497. Dr. A. Klöcker. Soil in environs of Carlsberg.   1920
One other strain.

Pseudosaccharomyces austriacus
492. Dr. A. Klöcker. *Alps Autr.* Soil, Austrian Alps.   1920

Pseudosaccharomyces corticis
485. Dr. A. Klöcker. *B. 60.* Bark, lichen, and moss from trees planted
in environs of Copenhagen.   1920

Pseudosaccharomyces germanicus
491. Dr. A. Klöcker. *Harz 3.* Soil, Harz Mountains.   1920

Pseudosaccharomyces indicus
487. Dr. A. Klöcker. *Himalaya.* Soil, Himalayas.   1920

Pseudosaccharomyces javanicus
498. Dr. A. Klöcker. *Java 104.* Soil, Java.   1920

Pseudosaccharomyces jenseni
494. Dr. A. Klöcker. *Java 403.* Soil, Java.   1920

Pseudosaccharomyces lefari
489. Dr. A. Klöcker. *Java 105.* Soil, Java.   1920

Pseudosaccharomyces malaianus
484. Dr. A. Klöcker. *Java 104 a.* Soil, Java.   1920

Pseudosaccharomyces mülleri
496. Dr. A. Klöcker. *Java 201.* Soil, Java.   1920

Pseudosaccharomyces occidentalis
486. Dr. A. Klöcker. *St. Croix.* Soil, St. Croix, W.I.   1920

Pseudosaccharomyces santacruzensis
493. Dr. A. Klöcker. *St. Croix 409.* Soil, St. Croix, W.I.   1920

Pseudosaccharomyces willi
488. Dr. A. Klöcker. *St. Thomas 193.* Soil, St. Thomas, W.I.   1920

Rhizopus japonicus
604. A. Jörgensen's Lab., Copenhagen. *Thaysen.*   1920

Rhizopus nigricans
956. Prof. A. K. Ling, Birmingham University. *Ling.*   1921

Saaz Yeast. See *Yeast (Saaz)*

Saccharomyces anomalus. See *Willia anomala*

Saccharomyces apiculatus Hansen. See *Pseudosaccharomyces apiculatus*
Reess.

Saccharomyces carlsbergensis Hansen
742. Dr. A. Klöcker, Carlsberg Lab. *Carlsberg.* (*Compt. rend. de trav.
du Lab. Carlsberg,* 1900, **5**, 1.)   1920

Saccharomyces cerevisiae Hansen
466. Dr. A. Klöcker, Copenhagen. *Carlsberg.*   1920
381. Carlsberg Lab. *21.* Brewing yeast.   1920
815. Prof. Harden, Lister Inst. Baker's yeast.   1921

Saccharomyces ellipsoideus. (Syn. *Saccharomyces ellipsoideus I*)
  467. Dr. A. Klöcker. *Carlsberg.*   1920
      One other strain.

Saccharomyces ellipsoideus II.   See *Saccharomyces turbidans*

Saccharomyces exiguus
  812. Prof. Harden, Lister Inst. *Harden.*   1921

Saccharomyces farinosus.   See *Pichia farinosa.*

Saccharomyces fragilis
  905. A. Chaston Chapman, F.R.S. *Armstrong-Chapman.* Isolated from
      kefir by Jörgensen. (*Die Mikroorg. d. Gärungs-Industrie*,
      1918, 276.)   1921

Saccharomyces intermedius
  469. Dr. A. Klöcker. *Carlsberg.*   1921

Saccharomyces marxianus
  472. Dr. A. Klöcker. *Carlsberg.*   1920

Saccharomyces monacensis Hansen
  743. Dr. A. Klöcker. *Carlsberg.* (*Compt. rend. de trav. du Lab. Carls-
      berg*, 1900, **5**, 1.)

Saccharomyces pastorianus. (Syn. *Saccharomyces pastorianus I*)
  468. Dr. A. Klöcker. *Carlsberg.*   1920

Saccharomyces pastorianus II.   See *Saccharomyces intermedius*

Saccharomyces pastorianus III.   See *S. validus*

Saccharomyces saké
  1015. Prof. Ling, F.I.C., Birmingham. *Ling.* Isolated from saké. 1921

Saccharomyces thermantitonum Johnson, 1905
  790. Jörgensen. *Jörgensen.* (*Biochem. Ztschr.*, 1919, **97**, 156.) 1921
  791. Institut f. Gärungsgewerbe, Berlin. *Berlin.* (*Biochem. Ztschr.*,
      1920, **102**, 258.)   1920
  792. A. Chaston Chapman, F.R.S. *Chapman.* Believed to be descended
      from Johnson's original strain, 1905.   1921

Saccharomyces turbidans
  471. Dr. A. Klöcker. *Carlsberg.*   1920

Saccharomyces validus
  470. Dr. A. Klöcker. *Carlsberg.*   1920

Saccharomyces.   See also *Yeast*

Saccharomycoides ludwigii
  473. Dr. A. Klöcker.   1920

Saccharomycopsis capsularis
  814. Prof. Harden, Lister Inst. *Harden.*   1920

Salmonella, type Arkansas.   See *B. suipestifer* (No. 179)
          type Binns. See *B. suipestifer* (Nos. 73 and 175)
          type G. See *B. suipestifer* (No. 91)
          type Hirschfeld. See *Bacillus from Hog cholera, B. paratypho-
          sus C, B. suipestifer* (No. 352), *B. suis* (No. 426), *B. typhi
          suis, B. voldagsen*
          type Mutton. See *B. anatum, B. psittacosis, Bacillus of
          Schweinpest, B. suipestifer* (Nos. 74, 115, 178, 32, 106, 959),
          B. suis (No. 425), *Bacillus of swine typhus*
          type Newport. *B. suipestifer* (Nos. 129 and 726)
          type Reading. *B. suipestifer* (No. 72)

Salmonella, type Schottmüller. See *B. paratyphosus B*
    type Stanley. See *B. suipestifer* (No. 92)
    unclassified serologically. See *B. abortivo-equinus*

Sarcina aurantiaca
  952. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *01346.*   1921

Sarcina lutea
  611. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.*   1920

Schizosaccharomyces mellacei
  1014. Prof. Ling, F.I.C., Birmingham. *Ling.*   1921

Schizosaccharomyces octosporus
  382. Carlsberg Lab. *13.*   1920

Schizosaccharomyces pombé Lindner
  902. A. Chaston Chapman, F.R.S. *Chapman.* The species was dis-
    covered by Saar in ' pombé ' (African millet beer).   1921

Schwanniomyces occidentalis Klöcker
  476. Dr. A. Klöcker. *Carlsberg.*   1920

Spirillum rubrum
  953. Dr. Houghton, Parke Davis Co., Detroit, U.S.A. *01348.*   1921

Sporothrix
  627. Capt. Edwards, R.A.V.C., Royal Vet. Coll., London. *25 Horse.*
    Abscess in leg of imported U.S. Army horse, 1915.   1920
    7 other strains from equine cases of sporotrichosis.

Sporotrichum councilmani
  882. Dr. K. F. Meyer. Isolated by Dr. Wolbach from a human case of
    sporotrichosis (acute arthritis of knee-joint following injury).
    (*J. Med. Research*, 1917, **36**, 337.)   1921

Sporotrichum gougeroti
  744. *New Zealand.* Isolated by Dr. Champtaloup in New Zealand from
    urine of patient with cystitis, 1912.   1920

Sporotrichum schenckii
  406. Hektoen. Original *Schenck-Hektoen.* Human case of sporotrichosis,
    1900. (*Johns Hopkins Hosp. Bull.*, 1898, **9**, 286.)   1920
    3 other strains of sporotrichum from human cases of sporo-
    trichosis.

Staphylococcus cereus flavus
  193. Lister Inst. *L.I.P.M.*   1920

Staphylococcus cremoris=viscosi
  963. Isolated by B. W. Hammer and W. A. Cordes, Dairy Dept., Iowa
    State Coll., U.S.A., from an outbreak of ropy milk, 1920.
    (*J. Dairy Sc.*, 1920, **3**, 291.)   1921

Staphylococcus epidermidis albus
  37. Lister Inst. *Huxley.* Sputum, 1911.   1920
    4 other strains.

Staphylococcus pyogenes
  186 A. (*aureus.*) *Eliza.* Isolated by Dr. C. J. Martin from abscess in
    neck of child, 1920.   1920
  36. (*albus.*) Lister Inst. *Galloway.* Case of vaginitis, 1911.   1920
  182. (*citreus.*) Lister Inst. *Moss.* Pimple on throat, 1915.   1920
    15 other strains.

Staphylococcus salivarius
189. Lister Inst. *Rayner.*   1920

Stemphylium ? sp.
1005. *Cotton (France).*   Isolated by Miss Lorrain Smith, F.L.S., Natural
      History Museum, S. Kensington, from rotting cotton canvas
      from France.   1921
1006. *Cotton (Dover).*   Isolated by Miss Lorrain Smith, F.L.S., from
      rotting cotton canvas from Dover.   .   1921

Streptococcus acidi lactici Grotenfeldt
662. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.* Milk.   1920

Streptococcus in animals
646. *62 A.* Isolated by Capt. Edwards, R.A.V.C., at Royal Vet. Coll.,
      London, from strangles lesion in a horse, 1918.   .   1920
645. *90 Foal Sparrow.* Isolated by Capt. Edwards from pus from knee-
      joint of foal with joint ill, 1919.   1920
648. *Cow Wardlaw.* Isolated by Capt. Edwards from contagious mastitis
      of cow, 1918.   1920
           11 other strains isolated from lesions of horses, cows, cats, and
           dogs.

Streptococcus bulgaricus
553. *Lind.* Isolated by Dr. C. Lind, Copenhagen, from specimen of
      Yoghurt obtained by him from Bulgaria, 1909.   1920

Streptococcus erysipelatis
226. Lister Inst. *L.I.P.M.*   1920

Streptococcus (faecal)
370. (*S. faecalis.*) Capt. S. R. Douglas. *Stubbs IV (Elstree 35).*   1920
775. (*Enterococcus.*) Pasteur Inst., Paris. *Tissier.*   1920
           5 other strains.

Streptococcus haemolyticus
Strains received from Dr. Avery, Rockefeller Inst. (J. Exper. M.,
                    1919, **30,** *179)*
325. Type S. 3. *3. 22.* Broncho-pneumonic lung, Texas, U.S.A., 1918.
                                                               1920
326. Type S. 23. *23. 20.* Throat, lobar pneumonia, Texas, 1918.
                                                               1920
327. Type S. 60. *60. 10.* Throat, measles, Texas, 1918.   1920
328. Type S. 84. *84. 18.* Pleural fluid, broncho-pneumonia, Texas,
      1918.   1920
           6 other strains.

Streptococcus (Havens' Groups)
Received from Dr. Havens, Iowa City, U.S.A. (J. Infect. Dis.,
                    1919, **25,** *315)*
461. Group 1. *No. 2.* Sputum, broncho-pneumonia, 1918.   1920
462. Group 2. *No. 3.* Acute bronchitis, 1918.   1920
464. Group 3. *No. 5.* Broncho-pneumonia, 1919.   1920
           One other strain of Group 2 (No. 463) and one other strain of
           Group 3 (No. 465).

Streptococcus ignavus
442. Dr. Barnes, California, U.S.A. *Barnes 11.* Sputum. (*J. Infect.
      Dis.,* 1919, **25,** 47.)   1920

Streptococcus infrequens
   438. Dr. Barnes. *Barnes 3.* Gastric ulcer. (*J. Infect. Dis.*, 1919, **25**,
          47.)   1920
              7 other strains.
Streptococcus rheumaticus Allen
   304. Dr. Allen. *Allen.* Blood, acute rheumatism and endocarditis, 1910.
                                                                                1920
Streptococcus rheumaticus Beattie
   227. Prof. Beattie. *Beattie.*   1920
Streptococcus salivarius
   445. Dr. Barnes. *Barnes 34.* Tonsillitis. (*J. Infect. Dis.*, 1919, **25**,
          47.)   1920
Streptococcus subacidus
   437. Dr. Barnes. *Barnes 1.* Blood. (*J. Infect. Dis.*, 1919, **25**, 47.)
                                                                                1920

Streptothrix
              Strains from Streptotrichosis in Man
   450. Dr. Gibson, Oxford. *Gibson.* Isolated 1914.   1920
   146. Lister Inst. *C.S.F.* Cerebro-spinal fluid, 1920.   1920
   658. Lister Inst. *Birt-Leishman.*   1920
              Strains from Streptotrichosis in Animals
   630. *24 Foal Blackwell.* Isolated by Capt. Edwards, R.A.V.C., Royal Vet.
          Coll., London, in pure culture from hock joint of foal.
                                                                                1920
   628. (*S. cameli* Mason.) Capt. Edwards, R.A.V.C. *Camel.* Isolated by
          Major Mason, R.A.V.C., from lung of Sudanese camel, 1917.
          (*J. Comp. Path. and Therap.*, 1919, **32**, 34.)   1920

Thamnidium elegans Link
   920. A. Chaston Chapman, F.R.S. *Chapman.*   1921
Timothy Grass Bacillus. See *B. phlei*
Torula
   886. Dr. K. F. Meyer. *2.* Isolated by Stoddart and Cutler in Boston,
              Mass., from human case of torula infection. (*Monog. Rocke-
              feller Inst. M. Research*, 1916, **6**.)   1921
   885. *1.* Isolated by Dr. K. F. Meyer from nasal tumour of a horse in
              Philadelphia, 1912.   1921
Torula (black)
   908. A. Chaston Chapman, F.R.S. *Chapman.*   1921
Torula (red)
   820. (*Torula rosea.*) Prof. Harden, Lister Inst. *Harden.*   1921
   241 A. (Pink Torula.) Dr. S. G. Paine, Imperial Coll. of Science,
              S. Kensington. *Paine.*   1920
   907. (Red Torula.) A. Chaston Chapman, F.R.S. *Chapman.*   1921

Trichophyton balcaneum
   704. Prof. Castellani. Isolated 1915.   1920
Trichophyton, &c.
              12 strains of organisms derived from tinea circinata, tinea
              tonsurans, dhobi itch, favus, &c., which have been only partly
              identified.

Trypanosoma brucei
   23 A. Prof. Ehrlich through Prof. Warrington Yorke, Liverpool School of
              Tropical Medicine. *Nagana ferox.*   1920

Trypanosoma equiperdum
18 A. Pasteur Inst., Paris. *Algeria.* Algerian strain.   1921

Trypanosoma lewisi
24 A. *Robertson.* Isolated by Miss M. Robertson, Lister Inst., from wild
      rats, 1920.   1920

Trypanosoma nigeriense
19 A. Miss M. Robertson. *West Africa.* Human case of trypano-
      somiasis, West Africa.   1920

Trypanosoma rhodesiense
28 A. Prof. Warrington Yorke. *Yorke.* Human case of trypanosomiasis.
                                                           1921

Vibrio cholerae
723. Col. Liston. *Liston 253.* Choleraic stool, Bombay, 1918.   1920
18. Dr. J. Freeman, St. Mary's Hosp. *Freeman 33.* Case of mild
      cholera in Russia, 1914.   1920
20. Dr. J. Freeman. *Kucera.* Isolated by Prof. Kucera, Hungarian
      epidemic, 1913.   1920
21. *Singapore.* Case from Straits Settlements.   1920
26. Col. Liston. *Liston.* Stool of Sepoy attacked on way to Persian
      Gulf, 1915.   1920
      12 other strains.

Vibrio El Tor
307. Dr. Crendiropoulo. *No. 4.* Isolated by Gotschlich from intestine
      of dysenteric patient at El Tor, 1905. (*Ztschr. f. Hyg. u.
      Infektionskrankh.*, 1906, **53**, 281.)   1920
55. Dr. Crendiropoulo. *A.*   1920
56. Král, Prague. *V.*   1920
      2 other strains of 'El Tor' Vibrios (Nos. 57 and 58) which do
      not agglutinate with cholera serum (see *Ztschr. f. Hyg. u.
      Infektionskrankh.*, 1906, **53**, 281).

Vibrio fetus Theobald Smith
384. *438.* Isolated by Prof. Theobald Smith. (*J. Exper. M.*, 1919,
      30, 299.)   1920

Vibrio Finckler-Prior
774. King's College, London.   1920

Vibrio from oysters
831. *B. 22–6.* Isolated by Mrs. Barratt at Lister Inst. from diseased
      East Coast oysters, 1920.   1921

Vibrio paracholerae
30. (*V. paracholerae* Martin No. 1.) Lt.-Col. Martin. Stool of con-
      valescent patient, Montazah, 1916.   1920
558. (*V. paracholerae A* Mackie and Storer, *J. Roy. Army Med. Corps*,
      1918, **31**, 161). Stool from choleraic case, Egypt, 1916.
                                                           1920
559. (*V. paracholerae B* Mackie and Storer.) Source as in No. 558.
                                                           1920
560. (*Vibrio K* Mackie.) Prof. Mackie. Choleraic case in Egypt, 1917.
                                                           1920
561. (*Vibrio Belah* Mackie.) Source as in No. 560.   1920
562. (*Vibrio Forrest* Mackie.) Source as in No. 560.   1920
261. (*Vibrio Nasik.*) Lister Inst. Isolated by Dr. Simond from a case of
      typical cholera in Nasik, India, 1903.   1920

Vibrio metchnikovi
262. Lister Inst. Originally isolated by Gamaleia from disease of fowls.
1920

Vibrio resembling *V. cholerae*
719. Col. Liston. *Liston 128.* Water, Bombay. 1920
17 strains besides this and others under special names.
See also *Spirillum rubrum.*

Vibrion septique Pasteur and Joubert, 1877
548. Type I. Miss M. Robertson. *Brissons.* Isolated by Capt. Henry from case of gas gangrene. 1920
282. Type II. Miss M. Robertson. *Bedford.* Amoebic abscess of brain. 1920
284. Type III. Miss M. Robertson. *George A. 2.* Case of gas gangrene developing upon surgical treatment of a healed wound. 1920
286. Type ' Jerral '. Capt. Armitage. *Jerral.* Septic wound without gas gangrene. 1920
One other strain (No. 547) of Type I : 3 other strains of Type II : 4 other strains of Type III.

Willia anomala
474. Dr. A. Klöcker, Carlsberg Lab. *Carlsberg.* 1920
Willia saturnus Klöcker
475. Dr. A. Klöcker. *Carlsberg.* 1920

Yeast (Frohberg)
903. A. Chaston Chapman, F.R.S. *Chapman.* Isolated by Lindner from yeast from Frohberg's Brewery at Grimma, Saxony. 1921
Yeast (Kefir) Hansen
904. A. Chaston Chapman, F.R.S. *Chapman.* 1921
Yeast (Lactose-fermenting)
607. Dr. A. Thaysen, Holton Heath, Dorset. *Thaysen.* St. Ivel cheese.
1920
Yeast (Logos)
909. *Ling.* Isolated previous to 1895 by H. van Laer and Denamur from pitching yeast used at Logos & Co.'s Brewery, Rio de Janeiro. Origin unknown, probably sugar-cane. Received by Dr. Raistrick from Prof. Ling, 1920. (*Moniteur scient.*, 1895, July, 499.) 1921
Yeast (Saaz)
906. A. Chaston Chapman, F.R.S. *Chapman.* Isolated by Lindner at Institut für Gärungsgewerbe, Berlin, from pitching yeast used in the municipal brewery at Saaz, Bohemia. 1921
Yeast (Sternberg ' 675 ')
608. Dr. A. Thaysen. *Thaysen.* Used in U.S.A. for manufacture of glycerine. 1920
Yeasts, apiculate. See *Pseudosaccharomyces*

Zopfius zenkeri. See *B. proteus zenkeri*
Zygosaccharomyces barkeri
813. Prof. Harden, Lister Inst. *Harden.* 1921

PART II. LIST OF SUBJECTS

WITH REFERENCES TO THE RELATED ORGANISMS

ABORTION in cattle and pigs
    B. abortus
    Vibrio fetus
    in horses
    B. abortivo-equinus

ACETIC ACID, organism used in manufacture of, from pentoses
    Lactobacillus pentoaceticus
    see also Vinegar

ACETONE, organism used in manufacture of
    B. butylicus

ACID-FAST BACILLI
    Bacilli from butter
    Bacillus from Leprosy.
    B. johne
    B. phlei
    B. smegmatis
    Marpmann's bacillus
    Möller's ' Mist ' bacilli
    see also Tuberculosis

ACNE
    B. acnes

ACTINOBACILLOSIS
    Actinobacillus

ACTINOMYCOSIS in animals
    Actinomyces caprae
    &c. in man
    Actinomyces bovis
    Actinomyces (Nos. 434 and 600)
    Nocardia lutea

AIR : *see* Soil, Air, Water, &c., organisms from

ANAEROBES, pathogenic : *see* Botulism, Gas gangrene, Necrobacillosis, Rauschbrand, Tetanus

ANTHRAX
    Anthracoid bacillus
    B. anthracis

BEANS, disease of
    Pseudomonas phaseoli

BLACK ROT of cauliflower
    Pseudomonas campestris

BLASTOMYCOSIS in animals
    Torula (No. 885)
    in man
    Blastomyces (Nos. 271 and 272)
    Torula (No. 886)

BOTULISM
    B. botulinus

BREAD, ROPINESS IN
    B. mesentericus panis viscosi
    B. mesentericus (Jordan Lloyd's types)

BRUCELLOSIS
    B. abortus
    B. melitensis
    B. paramelitensis

BUTTER, acid-fast bacilli from
    Bacilli from butter

BUTYL ALCOHOL, organism used in manufacture of
    B. butylicus

CABBAGE OR TURNIP ROT
    B. caratovorus

CANVAS ROT, organisms associated with
    Alternaria ? sp.
    Botrytis ? sp.
    Diplodiella ? sp.
    Stemphylium ? sp.

CEREBRO-SPINAL MENINGITIS
    Meningococcus

CHEESE, fungi of
    Penicillium album camemberti
    P. brevicaule
    P. camemberti
    P. roqueforti
    micro-organisms of
    B. güntheri
    Emmentaler Coccus
    Yeast(lactose-fermenting) No.607

CHOLERA
    Vibrio cholerae
    V. El Tor
    see also Paracholera

COCCIDIODAL GRANULOMA
 Coccidiodes immitis
CONJUNCTIVITIS
 Koch-Weeks' bacillus
 chronic
 Leptothrix
COLIFORM TYPES from various sources
 B. acidi lactici
 B. cloacae
 B. coli communis
 Bacillus (coliform)
 B. communior
 B. lactis aerogenes
 B. neapolitanus
 B. ozaenae
 B. putrificus coli
 Leather bacillus
CYSTITIS, organisms isolated from
 cases of
 Bacillus (coliform)

DHOBI ITCH
 Trichophyton
DIARRHOEA, white, of chicks
 B. pullorum
 see also Fowl typhoid
DIARRHOEAL CONDITIONS other than
 cholera, organisms associated with
 B. asiaticus
 B. columbensis
 B. faecalis alcaligenes
 B. Morgan No. 1
 B. proteus
 B. pyocyaneus
 B. Schmitz
DISTEMPER, organisms associated with
 B. bronchisepticus
 Distemper bacillus
DIPHTHERIA
 Corynebacterium diphtheriae
DIPHTHEROID organisms from animals
 Corynebacterium flavidum
 C. lipolyticum
 C. pseudotuberculosis
 C. pyogenes
 Diphtheroids
 from man
 Corynebacterium coryzae seg-mentosum
 C. hofmanni
 C. ixerosis
DYSENTERY, bacillary
 B. dysenteriae

ENTERIC FEVER
 B. typhosus

ENTERITIS in calves
 B. paracoli
 in man
 B. enteritidis Gärtner (N 127)
ERYSIPELAS, swine
 B. erysipelatis suis
EYE DISEASES, Koch-Weeks' bacillus

FAVUS
 Trichophyton
FERMENTATION industries, micro-
 organisms associated with
 Amylomyces (various species)
 Aspergillus „
 B. acetoethylicum
 B. butylicus
 B. volutans
 Citromyces B.
 Debaryomyces globosus
 Hansenia apiculata
 Hanseniaspora valbyensis
 Lactobacillus pentoaceticus
 Monilia candida (No. 922)
 Mucor (various species)
 Mycoderma cerevisiae
 Oidium lactis
 Penicillium (various species)
 Pichia „
 Pseudosaccharomyces (various species)
 Rhizopus (various species)
 Saccharomyces „
 Saccharomycoides ludwigii
 Saccharomycopsis capsularis
 Schizosaccharomyces (various species)
 Schwanniomyces occidentalis
 Thamnidium elegans
 Torula (Nos. 241A, 820, 907, 908)
 Willia (various species)
 Yeast (Nos. 608 and 904)
 Zygosaccharomyces barkeri
FISH DISEASES
 Bacillus from trout
FLAX, organism associated with
 disease of
 Polyspora
FOOD-POISONING in man
 B. aertrycke
 B. enteritidis Gärtner (Nos. 125, 126)
 B. paratyphosus C (No. 749)
 B. suipestifer (Nos. 72, 73, 74, 115, 129, 178)

FOWL TYPHOID
    B. sanguinarium
    B. gallinarum
    see also Diarrhoea, white, of chicks
FUNGI, tropical, associated with lesions of epidermis and epidermal appendages
    Acladium castellani
    Endodermophyton indicum
    Epidermophyton rubrum
    Hemispora rugosa
    Monilia kruzei
    M. macedoniensis
    M. pinoyi
    M. tropicalis
    M. zeylanici
    Oidium asteroides
    O. rotundatum
    Trichophyton balcaneum

GAS GANGRENE, anaerobes liable to cause
    B. fallax
    B. histolyticus
    B. oedematiens
    B. welchii
    Vibrion septique
  anaerobes whose action may be ancillary to condition of
    B. aerofetidus
    B. bifermentans
    B. cochlearius
    B. parasporogenes
    B. sphenoides
    B. sporogenes
    B. tertius
    B. tetanomorphus
GLANDERS
    B. mallei
GONORRHOEA
    Gonococcus
GUINEA-PIG EPIZOOTIC
    B. paratyphosus B (No. 959)
    B. caviae

HAEMORRHAGIC SEPTICAEMIA: see Septicaemia, haemorrhagic
HOG CHOLERA
  Bacillus from hog cholera
    B. suipestifer (No. 179)
HYACINTH BULBS, Wakker's disease of
    Pseudomonas hyacinthi

INFLUENZA, organisms associated with
    B. influenzae
    Mather's Coccus

JOHNE'S DISEASE
    B. johne
JOINT ILL in foals
    B. viscosum equi
    Streptococcus (No. 645)

KALA-AZAR
    Leishmania donovani

LEATHER, organism causing black and dark green spots on
    Fumago (No. 968)
LEPROSY
    B. leprae
LYMPHANGITIS, epizootic, in horses
    Cryptococcus farcinosus
  ulcerative, in horses
    Corynebacterium pseudotuberculosis

MADURA FOOT
    Nocardia indica
MALTA FEVER
    B. melitensis
    B. paramelitensis
MASTITIS, contagious, in cows
    Streptococcus (No. 648)
MEASLES, organisms associated with
    Diplococcus (No. 407)
MILK and milk products, micro-organisms of
    B. bulgaricus
    B. güntheri
    Emmentaler Coccus
    Streptococcus acidi lactici
    S. bulgaricus
    Yeast (lactose-fermenting) (No. 607)
  ropiness in
    Staphylococcus cremoris-viscosi
MULBERRY, disease of
    B. mori
MUSHROOM, brown spot disease of
    Pseudomonas tolaasi
MYCETOMA
    Nocardia indica

NECROBACILLOSIS
    B. necrophorus

ORIENTAL SORE
    Leishmania tropica

PARACHOLERA
    Vibrio paracholerae

PARATYPHOID A FEVER
B. paratyphosus A
—— B FEVER
B. paratyphosus B (*Salmonella*, type Schottmüller)
—— C FEVER
B. paratyphosus C (*Salmonella*, type Hirschfeld)
PASTEURELLOSIS : *see* Plague *and* Septicaemia, haemorrhagic, in animals
PEAR BLOSSOM BLIGHT
Pseudomonas barkeri
PLAGUE
B. pestis
PLANTS, bacteria causing diseases of
Aplanobacter michiganense
B. caratovorus
B. lathyri
B. mori
B. solanisaprus
B. vesicatorum
Pseudomonas barkeri
Ps. campestris
Ps. hyacinthi
Ps. phaseoli
Ps. proteomaculans
Ps. tolaasi
PNEUMONIA
Pneumococcus
PROTOZOA
Colpidium colpoda
Leishmania donovani
L. tropica
Trypanosoma brucei
T. equiperdum
T. lewisi
T. nigeriense
T. rhodesiense
PYELONEPHRITIS in cattle
Corynebacterium pyogenes

RAUSCHBRAND (quarter ill)
B. chauvoei
RESPIRATORY TRACT, Gram-negative cocci from
Micrococcus catarrhalis
M. flavus
M. pharyngis siccus
ROPINESS in bread
B. mesentericus (Jordan Lloyd's types)
B. mesentericus panis viscosi
in milk
Staphylococcus cremoris-viscosi

SALMONELLOSIS
B. abortivo-equinus
B. caviae
B. enteritidis Gärtner
B. gallinarum
Bacillus from hog cholera
B. paratyphosus B
B. paratyphosus C
B. psittacosis
B. pullorum
B. sanguinarium
Bacillus of Schweinpest
B. suipestifer
B. suis
Bacillus of swine typhus
B. typhi suis

SAN JOAQUIN VALLEY DISEASE
Coccidiodes immitis

SEPTICAEMIA, haemorrhagic, in animals
B. avisepticus
B. bovisepticus
B. cuniculisepticus
B. ovisepticus
B. pseudotuberculosis rodentium
B. suisepticus
Pasteurella

SEPTICAEMIC processes (boils, abscesses, &c.)
Micrococcus tetragenus
Staphylococcus (various species)
Streptococcus   ,,

SKUNK EPIZOOTIC
B. suipestifer (No. 106)

SOIL, AIR, WATER, DUST, &c., organisms from
Acrostalagmus cinnabarinus
Actinomyces (No. 390)
B. dendroides
B. fluorescens
B. herbicola
B. megatherium
B. mesentericus
B. mycoides
B. prodigiosus
B. subtilis
B. violaceus
Nocardia dessenviller
Pseudomonas radicicola
Pseudomonas (denitrifying)
Sarcina aurantiaca
S. lutea
Vibrios from water, &c.

Soy BEAN, organism from nodule of
   root of
   Pseudomonas radicicola
SPOROTRICHOSIS in animals
   Sporothrix
 in man
   Sporotrichum councilmani
   S. gougeroti
   S. schenckii
SPRUE, organisms associated with
   Monilia ? psilosis
   Parasaccharomyces ashfordi
STRANGLES in horses
   Streptococcus (No. 646)
STREPTOTRICHOSIS in animals
   Streptothrix (No. 630)
   S. cameli
 in man
   Streptothrix (Nos. 146, 450, and
   658)
SWINE FEVER
   Bacillus of Schweinpest
——— TYPHUS
   Bacillus of swine typhus

TETANUS
   B. tetani
THRUSH
   Monilia albicans
TIMOTHY GRASS, bacillus of
   B. phlei
TINEA CIRCINATA
   Trichophyton
——— TONSURANS
   Trichophyton
TOMATO, Grand Rapids disease of
   Aplanobacter michiganense
TOMATO CANKER
   B. vesicatorium
TORULA infection in man
   Torula (No. 886)
TRYPANOSOMIASIS
   Trypanosoma brucei
   T. equiperdum
   T. lewisi
   T. nigeriense
   T. rhodesiense
TUBERCULOSIS, amphibian
   B. tuberculosis (No. 946)

TUBERCULOSIS, avian
   B. tuberculosis (Nos. 51, 224 A,
   and 919)
———, bovine
   B. tuberculosis (Nos. 46, 47, 49,
   918)
———, human
   B. tuberculosis (Nos. 48, 50, 52,
   914, and 917)
TURNIP OR CABBAGE ROT
   B. caratovorus
TYPHOID FEVER
   B. typhosus
   see also Fowl typhoid
TYPHUS FEVER, organism associated
   with
   B. typhi exanthematici
   see also Swine typhus

ULCERATIVE LYMPHANGITIS in horses
   Corynebacterium pseudotuberculosis
UNDULANT FEVER
   B. melitensis
   B. paramelitensis

VINEGAR, organisms associated with
   manufacture of
   B. aceti
   B. kützingianum
   B. pasteurianum
   Bacterium from vinegar
   see also Acetic acid

WATER : see Soil, Air, Water, Dust,
   &c., organisms from
WEIL'S DISEASE
   Leptospira icterohaemorrhagiae
WEIL-FELIX REACTION
   B. proteus vulgaris X. 19 (No. 67)
WHOOPING-COUGH
   B. pertussis

YEAST, baker's
   Saccharomyces cerevisiae (No. 815)
 brewer's
   Saccharomyces cerevisiae (No. 381)
   Yeast (Frohberg, Logos, and
   Saaz)
YELLOW FEVER
   Leptospira icteroides

MEDICAL RESEARCH COUNCIL

no. 65

FIRST REPORT OF THE

MINERS' NYSTAGMUS COMMITTEE

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CONTENTS.

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INTRODUCTION, WITH A SUMMARY OF THE PRIMARY CONCLUSIONS OF THE COMMITTEE.

SINCE the date of their appointment in 1920 by the Medical Research Council, at the request of the Home Office and upon the recommendation of the Miners' Lamps Committee, the Miners' Nystagmus Committee have been engaged in investigating the causation and means of prevention of miners' nystagmus, which is an affection of the eyes occurring among coal miners. A detailed account of the main part of these investigations, together with a summary of previous investigations, will be found in the accompanying reports by Dr. T. Lister Llewellyn and Dr. W. H. R. Rivers. A further report by Mr. G. H. Pooley on the relation of errors of refraction in the eye to this disorder is in preparation.

The Committee have had placed at their disposal by the Miners' Lamps Committee the opinions expressed by the expert witnesses before that body upon the relationship of miners' nystagmus to illumination in mining work. Extracts from this evidence have been included in the following report by Dr. Llewellyn and are indicated by the letters M.L.C. (Miners' Lamps Committee). Statistical information has been obtained from the Home Office and the Mines Department. The Committee are also indebted for statistical information to the large Coal Owners' Mutual Indemnity Societies, and for this they would especially thank Mr. Binns for the Midlands, Mr. Fisher for South Wales, Mr. Gillhespy for Yorkshire, and the Yorkshire Miners' Union, for their help.

The investigations already undertaken have included:

The clinical examination by Dr. Llewellyn of two thousand cases from all parts of the kingdom;

Investigations by Mr. Pooley of the relationship of miners' nystagmus to errors of refraction ;

Studies by Dr. H. W. Eddison of the psycho-neurotic factors of the disease in Yorkshire, North Staffordshire, and South Wales ;

Visits by Dr. Llewellyn to collieries showing a high incidence rate of the disorder, with examinations of the cases and investigations of the working conditions underground ;

Photometric tests made underground with the lamps in general use.

Research grants have been made by the Medical Research Council, upon the recommendation of the Committee, to provide for these investigations.

Experiments have been carried out under the auspices of the Committee at several collieries on the use of electric cap lamps. A conference for discussion was held at Stoke with representatives of the management and miners at the collieries there, and of the Miners' Lamps Committee.

The Committee desire to express their thanks more particularly to the management of the Stafford Coal and Iron Company, the Shelton Iron, Steel, and Coal Company, the Sneyd Colliery Company, and the Chatterly Whitfield Company, for the help they have rendered in the course of these experiments.

The Committee have unanimously reached the following conclusions :

1. The essential factor in the production of miners' nystagmus is deficient illumination. Other factors, such as position during work, accidents, alcoholism, infections, malnutrition, hereditary predisposition, and errors of refraction, are of secondary importance only, while depth of workings, thickness of seams, and the ordinary gaseous impurities in mine air have no direct influence on the disease.

2. The deficient illumination is due to the low illuminating power of the safety lamps generally used by coal miners, to the distance at which these lamps have to be placed from the objects which the miner has to look at, and to the great absorption of light by the coal and the coal-dust covered surfaces. In addition the effect of coal-dust or dirt in obscuring the lamp glasses, the choking of the wire gauze chimneys, and the presence of moisture or low oxygen percentage in mine air, all reduce the light given by oil lamps, while failing voltage, poor bulbs, or lack of proper attention, have similar effects on the illumination given by electric lamps.

3. Workers at the coal face are more affected than other underground workers, and this appears to be due to the unrelieved blackness of the coal and the greater need for accurate vision.

4. Distinct signs of nystagmus are present in a large proportion of coal miners, though only in a small proportion do the symptoms ever become so severe as to cause even temporary incapacity for work underground.

The Committee recommend that since incapacity due to nystagmus is rare among coal miners working with open lights, everything possible should be done to make the standard of illumination of the objects looked at by the miner equal to that of an open-light pit. This can be effected at the coal face and elsewhere either by greatly increasing (to about two or three candles) the illuminating power of safety lamps as ordinarily used, or by the use of an electric light capable of being fixed on a miner's head, belt, or other convenient position, so that the light is automatically brought nearer the working area and does not impair clear vision by shining directly into the eyes. At parts of the pit other than the coal face the visibility of objects can be greatly increased by whitewashing, as well as by the stone dusting now obligatory for the prevention of explosions. The Committee believe that by the application of these remedies miners' nystagmus of sufficient severity to cause disablement can, by degrees, be entirely prevented.

During their investigations the Committee have noticed the prevailing belief among coal miners that miners' nystagmus causes permanent damage to, or even total loss of sight, if underground work is continued after the onset of symptoms. This belief, which is entirely erroneous, has led to much unnecessary suffering and to the development of psycho-neurotic symptoms in many cases. The disablement resulting leads to great loss to the miners, and increases the charges on the industry and general public.

The Committee recommend that both workman and employer be granted power to appeal to the medical referee, at intervals of not less than six months from the original certificate of disablement or date of last appeal, to assess the incapacity present. In this appeal the medical referee should certify that the man is either:

    1. Totally incapacitated.
    2. Partially incapacitated.
        a. fit for surface work.
        b. fit for suitable work below ground.
    3. Not incapacitated.

The Committee are continuing their work in investigating the causation of the disease and in studying the operation underground of remedial measures, with a view to assisting as far as possible the introduction and trial of new measures.

> J. S. HALDANE (*Chairman*).
> EDGAR L. COLLIS.
> G. H. POOLEY.
> W. H. R. RIVERS.
> T. LISTER LLEWELLYN (*Secretary*).

14 *December* 1921.

GENERAL REPORT ON MINERS' NYSTAGMUS

BY

T. LISTER LLEWELLYN, M.D., *Secretary to the Committee.*

CONTENTS.

I. Definition.

MINERS' nystagmus is an occupational disease of the nervous system which is confined to workers in coal mines, and in ironstone mines where on account of the presence of thin coal seams safety lamps are used. The chief symptom and physical sign is a rotatory oscillation of the eyeballs.

The word nystagmus is derived from the Greek νυσταγμός, meaning a nodding of the head as in sleep.

The disease was added to the Third Schedule of the Workmen's Compensation Act, 1906, by order of the Secretary of State on May 22, 1907.

Third Schedule.

Description of Disease or Injury.	Description of Process.
(12) Nystagmus.	Mining.

Altered July 30, 1913, to

(17) The disease known as Miners' Nystagmus, whether occurring in miners or others, and whether the symptom of oscillation of the eyeballs be present or not.	Mining.

II. Historical Survey of the Disease.

Justice cannot be done in a short account to the work of the numerous observers who have devoted their time to the study of the disease, and the object of this survey is to direct attention to the original papers.

Although the first case was described by Decondé (9, 10) in 1861 in a paper dealing with nystagmus generally, Snell (45) says that a Dr. Gillet of Sheffield recognized the disease in 1854. C. Turner Thackrah (50), writing of colliers in 1832, says: 'Their eyes, from swelling of the lids, appear small, are affected with chronic inflammation and intolerant of full light, and many, after a few years' trial, are obliged, by the injury which their health has sustained, and especially by the weakness of their eyes, to leave the mine.' Nieden (27) says that Peppmuller described cases in the period 1860–3. In 1875 C. Bell Taylor (49) published a paper on 'Miners' Nystagmus, a New Disease', in which he held the condition to be due to the overburdening of the eye muscles and to the sustained effort to see in a deficient light.

Opinions as to the causation of the trouble now began to diverge. From 1875 onwards the views of Snell and Dransart (11), that the disease was the result of the constrained position assumed at work and the upward direction of vision, obtained prominence and general acceptance. Snell (45, p. 97) says: 'The position of the miner at work is therefore the prime and essential cause of miners' nystagmus.' Nieden (27, 1894) held the causes to be in the first

place lack of light, but found the disease in those workers who were compelled to work in a constrained position with visual regard directed upwards. Nuel (29, 30, 1908) held the darkness of the mine and the crystalline fracture of the coal to be factors of equal importance with that of constrained position.

In direct opposition to these views Romiée (38, 39) from 1878 and Court (6, 7) from 1891 held that deficient light was the essential factor in the production of the disease.

The rival schools held numerous discussions in England, Belgium, and France, and the debates were carried on with spirit and more than a suspicion of acrimony.

An elaboration of the strained position standpoint was made in 1887 by Jeaffreson (19) and has been maintained from 1908 to the present time by Rutten (40–3). Both these observers hold the disease to be a neurosis brought about by the fatigue which follows the disassociation of movements normally combined, e. g. flexion of the head with elevation of the eyes. Christie Reid (37, 1906) attributes the disease to imperfect fixation and frequent disturbances of position. Poisoning by absorption of gases given off by the coal has been suggested by Pechdo (35, 1893) and tentatively by Harrison Butler (3, 1912), Coulter (5, 1914), and Leighton Davies (8, 1920). Failure of adaptation has been suggested by Weekers (52, 53, 1910). The labyrinthine origin of the disease was put forward by Peters (36) in 1907 and by Trombetta (51) in 1909.

The disease was brought into prominence in 1907, when the report of the Departmental Committee on Industrial Diseases (61) led to its inclusion among the scheduled industrial diseases of the Workmen's Compensation Act of 1906. In 1907 an official inquiry into the duration of working hours brought up the question before the Chamber of Representatives in Belgium. Nuel (28, 1907), in an important paper read before the Royal Academy of Medicine of Belgium, established clearly the claim of miners' nystagmus to be considered as an industrial disease causing real incapacity. An important discussion held at Brussels in 1908 did not bring any unanimity of opinion as to the causation of the disease, and as a result of this discussion Stassen was authorized by M. Libert, Chief Inspector of the mines of the Liège district, to carry out an official inquiry into the frequency of the disease in that coalfield.

Up to 1910 the constrained position at work was generally held to be the chief factor in the production of the disease. From this date another generation of workers come into prominence and the pendulum of opinion has swung full round to the acceptance of the views so stoutly held by Romiée and Court. In 1912 the Oxford Ophthalmological Congress (56) passed a resolution that the chief factor in the disease was the deficient light present in the mine —after a discussion in which the leading English authorities took part.

The work of Elworthy, Llewellyn, Ohm, and Stassen has confirmed this finding. Not until actual photometric measurements of the amount of light falling on the coal face had been published by Llewellyn was it realized in what a low illumination the miner worked. In his book, published in 1912, Llewellyn (22) gives the results of several years' investigation of the disease and his reasons

for thinking deficient light to be the chief factor in the production of the disease.

Coppez (4, 1912), from a study of the tracings of the nystagmic movements, comes to the conclusion that the nystagmus is due to an incomplete tetanus and is the result of fatigue. This fatigue is not solely found in the elevator muscles of the eye, but in the movements of elevation and convergence.

Dransart (12, 1913), although still holding that the *causa causans* is the direction of gaze, thinks deficient light to be a secondary cause and that with improved illumination the primary cause will disappear. Wilson (54, 55, 1913, 1915) holds that 'the feature common to ordinary and miners' nystagmus is imperfection of the retinal images'. In his Milroy Lectures, 1914, Shufflebotham (44) gives an interesting account of the disease. He considers the disease to be due to deficient light, cramped position, refractive errors, and ocular injuries at work.

In 1914, at the Royal Society of Medicine, London (57), the sections of neurology, ophthalmology, and otology held a joint meeting in which the relationship between general nystagmus and miners' nystagmus was discussed.

Stassen (46), as the result of the investigation referred to above, lays great stress on the physical conditions of work : the shock of increased atmospheric pressure when the cage containing the miners is rapidly lowered ; the sudden plunge into darkness before dark adaptation of the eyes is complete ; the ocular strain from the effort of working in a bad light ; the struggle between the two visual fields, each eye fixing a different facet of the crystalline fracture of the coal : all these factors producing a nervous syndrome characterized by inco-ordination and exaggeration of the visual reflexes. 'The nystagmus of miners is only the clinical manifestation of fatigue in the execution of ocular movements.' After a complete investigation of the conditions of work, influence of accident, ocular defects, age, height, hereditary predisposition, and conditions of lighting, he comes to the final conclusion : 'La cause nécessaire et suffisante des troubles visuels des ouvriers mineurs est le travail prolongé dans de mauvaises conditions d'éclairage' (46, p. 166). 'Le fait est donc certain : les troubles visuels des mineurs relèvent de la physiologie de la fatigue, dans de mauvaises conditions d'éclairage' (46, p. 184).

Ohm, Westphalia, has made valuable contributions to the study of the disease since 1910, notably in his books published in 1912 and 1916 (31). He has paid very great attention to the clinical and theoretical sides of the disease and has devised elaborate apparatus, including a double ophthalmoscope, for observing and for registering the nystagmic movements. It is impossible here to do justice to his exhaustive study of the tracings obtained. He does not consider accident, diseases of the eye, or refractive error to have any special influence ; but looks upon alcoholism, stature above the average, heterophoria, and deficient light sense as important predisposing factors. He sums up the influence of working conditions by saying that the disease varies directly with the amount of labyrinthine disturbance and inversely with the illumination

present. Miners' nystagmus is a disorder of tone, produced by the labyrinth, in different muscles or muscle groups. This disorder is caused by lack of light and other unfavourable conditions of work which bring about a too strong and too infrequent innervation of the labyrinth (31, p. 249). In 1920 (34) he writes, 'My last investigations confirm the importance of improved pit illumination'. He believes that a pit lamp giving 2–3 candle-power under unfavourable conditions would diminish the number of cases, and, after quoting Llewellyn's work, says : 'I can only add my voice to this cry for " More Light ".'

At the meetings of the North Staffordshire branch of the Institution of Mining Engineers at Stoke, 1920 (58); of the Illuminating Engineers, London, February 1920 (59) ; International Congress of the Royal Institute of Public Health, Brussels, May 1920 (60), discussions took place on papers presented by Llewellyn to which references will be made elsewhere.

Martin (26) holds that ' the disease is essentially one of exhaustion ', and thinks there is a similarity between cases of nystagmus and the anxiety neurosis of the war-strained.

Anderson (1), holding that ' astigmatism is by far the most frequent cause of miners' nystagmus ', suggests medical examination of all men before employment.

It is interesting to compare the modern view of the disease with that held formerly. At first considered to be a local myopathy of the elevator muscles of the eyes or the result of excessive accommodation—strictly local conditions—the modern teaching is that the disease is either a general fatigue of the whole oculomotor system or a general neurosis with special local manifestations in the oculomotor apparatus.
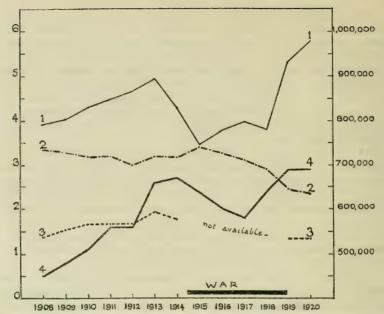
Miners' nystagmus is a disease of extraordinary complexity, and it is probable that the conditions which have at one time or another appeared to observers as the sole aetiological factor nearly all have an influence in the production of the disease.

III. Incidence of the Disease.

A. Economic Factors.

On May 22, 1907, miners' nystagmus was added to the schedule of industrial diseases in the Workmen's Compensation Act of 1906 ; before that date no accurate information of the prevalence of the disease is available. The number of cases receiving compensation has steadily risen since that year, with a big jump in 1913–14, when the definition of the disease was altered by order of the Secretary of State, July 30, 1913, from the original description, 'Nystagmus '— Process ' Mining ', to ' The disease known as miners' nystagmus, whether occurring in miners or others, and whether the symptom of oscillation of the eyeballs be present or not '. Table I and Graph I give statistics obtained from the Home Office, Mines Department, and Blue Books, ' Statistics of Compensation ', W. C. A.

Graph I.   Showing incidence of miners' nystagmus per 1,000 men ; output per year per underground workman in 100's of tons ; accident rate in Mining Industry per 100,000.

Curve 1.   Number of men employed underground.
,,   2.   Output per year per underground workman.
,,   3.   Accident rate per 100,000.
,,   4.   Incidence of fresh cases of miners' nystagmus per 1,000 underground workmen.

In curve No 4 the figures given for the years 1915–18 inclusive are only approximate.

TABLE I.   *Showing percentage incidence and number of cases receiving compensation for the first time during the year, total number of cases receiving compensation during the year, cost of all industrial diseases, number of men employed underground, number of cases disabled in the mining industry, and output per underground worker per year in tons.*

NYSTAGMUS.

FRESH CASES.

Year.	Percentage incidence.	Number.	Total No. of cases.	Cost of all industrial diseases. £.*	No. of men employed underground.	Accidents (1,000s).	Output. Tons per man per year.
1908	0·05	386	460	13,000	783,000	137	334
1909	0·08	631	1,011	26,000	805,000	154	328
1910	0·11	956	1,618	42,000	834,000	166	317
1911	0·16	1,375	2,519	68,000	849,000	167	320
1912	0·16	1,376	3,195	85,000	865,000	167	301
1913	0·26	2,402	4,551	113,000	895,000	195	321
1914	0·28	2,409	5,993	164,000	835,000	179	318
1915	0·24	1,780			743,000		341
1916	0·20	1,626			782,000	not	328
1917	0·18	1,461	not available		799,000	available	311
1918	0·24	1,917			783,000		291
1919	0·29	2,718	6 449	225,000	933,000	134	246
1920	0·29	2,865	7,028	343,000	978,000	134	235

* Home Office returns do not separate cost of nystagmus from other industrial diseases. Nystagmus is responsible for over 90 per cent. of this cost.

During the war years the Home Office did not insist on returns and the numbers given for these years are only approximate. It should be borne in mind that although there is an increase during the last two years, this increase is partly due to an accumulation of long-standing cases and possibly also to a recertification or resumption of payment to men who had failed after return to work. Of the 6,449 cases receiving compensation in 1919, 2,374 had been certified over a year; of these 1,431 had been certified over two years, and 478 over five years.

In Germany (18), from 1908–12, 18·2 per cent. of the invalidity claims on the Bochum Miners' Union were for nystagmus. The number of cases per 1,000 in the period 1905–9 was 3·29; from 1910–13, 3·25. In 1913, owing to a decision of the Superior Court, by which it was held that only serious cases of nystagmus were entitled to compensation, the number fell to 1·81. Stassen estimates that 0·2 per cent. of the Belgian miners suffer total incapacity from the disease (46, p. 163). Dransart (12) estimates the frequency in the North of France as 15 per cent., but 99 per cent. of these are unaware of the condition and are not incapacitated. The incapacity rate is 0·15 per cent. Although the figures for 1919 in the United Kingdom are higher than this, men on light work are included. It may be taken that the total incapacity rate in the four countries, United Kingdom, France, Belgium, and Germany, is 0·2 per cent. of men employed underground.

The number of men who show nystagmus on examination is much higher, and Stassen (46, p. 57), who has examined 11,000 miners, gives the percentage rate as 24·2. Nieden (27) found 5 per cent. in 27,982 miners, Romiée (39) and Nuel (28–30) give the frequency as 20 per cent., Llewellyn (22) 25 per cent., Court (6) 34·75 per cent. of all coal cutters examined.

B. Seasonal Prevalence of the Disease.

Many observers have noted that the disease is more prevalent in the dark winter months and that the bright summer months bring about improvement in the cases.

Table II. 2,371 cases. (*To end of November, 1921.*)

Cases arranged according to the Quarter of year in which failure took place.

	I	II	III	IV
Dransart & Famechon (13)	67	36	35	63
Ohm (31)	159	138	106	118
Llewellyn	565	310	373	401
	791	484	514	582
Percentage	33	20	22	25

C. Geographical Incidence in Great Britain.

A geographical analysis has been made from particulars supplied by the Home Office for the year 1919, and the result is shown graphically in the map.

The incidence is low in Scotland and in the naked-light districts of the Forest of Dean and Somerset, while North Staffordshire, Yorkshire, Cumberland, and the North Midlands give high rates. The low rate in Lancashire, where the pits are deep and safety lamps universally used, is striking, but there has been a great proportional increase in this district for the last few years, and possibly in a few years the incidence rate here will approach that of the neighbouring coalfields.

Mr. J. McGurk (Lancashire), Miners' Federation Representative : M.L.C. 'Cases are on the increase in Lancashire and there are hundreds of men now suffering from the disease and do not know it.'

D. Economic Loss.

The amount of compensation paid for all industrial diseases in the mining industry has risen from £13,382 in 1908 to £343,094 in 1920. This increase has been almost entirely due to nystagmus, and it may be assumed that in 1920 nearly £300,000 was paid in compensation for that disease alone.

The loss falls on workmen, employers, and the State. The workman, to whom health and working ability are everything, is reduced from an active life and a position of comparative affluence to dependence on weekly compensation. Home comforts are lost, the children are turned out into the world sooner, and the family tends to become restricted. The employer pays £300,000 a year in compensation, loses his best workmen, and finds his coal output reduced. The State loses the coal output of 6,000 men, which with the sum spent on compensation may be estimated at £1,000,000 a year. The indirect effect of shortage of coal on other industries must also be taken into account. For a fuller discussion of the question see Llewellyn (25).

IV. Description of the Disease.

The disease occurs in two forms, the latent and the manifest. In the former the patient has no symptoms, is unaware of the movement of his eyes, and suffers no disability. The manifest form may be divided into three types—the slight, in which there is little incapacity, the ordinary, in which underground work has to be given up, and the severe, in which incapacity is complete.

The first and most general subjective symptom is failure of sight, which is most marked at night-time or when the sufferer is called upon to perform the more skilled part of his work. He cannot notch timber and fails to drive his wedge or strike with the pick the exact piece of coal aimed at. He is unable to find his tools after he has placed them on the ground. This loss of sight
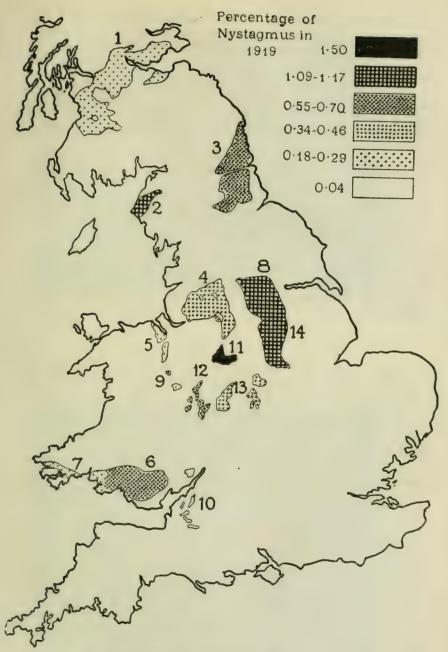
FIG. 1. Map showing areas of coalfields in Great Britain, and percentage incidence of cases of miners' nystagmus receiving compensation in 1919. (1) Scotland 0·18, (2) Cumberland 1·14, (3) Northumberland and Durham 0·55, (4) Lancashire 0·34, (5) N. Wales 0·29, (6) S. Wales 0·67, (7) West of Swansea 0·25, (8) Yorkshire 1·17, (9) Salop 0·27, (10) Bristol and Forest of Dean 0·04, (11) North Staffordshire 1·5, (12) South Staffordshire, including Cannock Chase 0·7, (13) South Midlands 0·46, (14) East and North Midlands 1·09.

4478   B

continues above ground and is most marked at night-time, in the early morning, and at dusk. The man also takes longer to 'get his sight', finds the journey to the coal face difficult, and is greatly annoyed by the bobbing up and down of the lights carried by his fellow workmen walking in front of him. He often has to sit down to let 'the lights go by', or if of a quarrelsome nature may even strike at a lamp which the man ahead is not shielding properly with a shade or by help of his body. Occasionally the first signs of the disease are bad timekeeping and deterioration of work, leading to friction with the officials.

Sleep is broken both by headaches and dreams; and gradually, but sometimes with startling suddenness, giddiness and temporary loss of sight follow exertion and stooping, and then the lamps and surrounding objects dance and revolve before the workman's eyes. The case is now well developed and the classical signs of headache, often most marked at the back of the head, giddiness on stooping or exertion, loss of sight especially at night-time, dread of lights, and sleeplessness become accentuated. Later on, after prolonged absence from work well-marked neurotic and even hysterical symptoms may appear. In these cases, although almost all objective signs have disappeared, the subjective symptoms remain well marked.

A. Symptoms.

Loss of Sight. In 1,330 cases in which it was possible to carry out a test of visual acuity, 54 per cent. possessed less than 6/12 vision in the acute stage of the disease. The test was only taken when oscillation of the eyes was absent. Ohm (31), after an examination of 532 cases, found that 75 per cent. had at least 6/12 vision. Stassen (46) found 25 per cent. of 20,000 miners chosen at random showed some sign of ocular fatigue.

The loss of sight is usually more marked at night-time, and men notice that their sight fails in 'twilight or when the lamps are lighted'. Night-blindness is sometimes so marked that men working on the afternoon shift have to be met at the pit top by their wives or children and led home. This loss of sight appears to be due to a failure of dark adaptation, and men in the early stages of the disease find it difficult to 'get their sight' when starting work ; and when the disease is advanced and the man persists in working, it is common for the workman to be led from the pit shaft to the coal face by his comrades. Once at the coal face he is able to win coal and satisfy his officials. This failure of dark adaptation or night-blindness has received attention from many observers—notably Weekers, Ohm, and Stassen. It is undoubtedly one of the most characteristic symptoms of the disease.

Movements of the Eyes. Sooner or later the man notices movements of surrounding objects and speaks of the lamps dancing before the eyes. Although this symptom is pathognomic when present, many men with well-marked oscillation have no subjective sensation of movement. The movement is usually described as wheel-like—'the lamps go round'—but some men say the lamps

Fig. 3.—Mental Depression in Miners' Nystagmus.

Fig. 2.—An Extreme Case of Photophobia.

Fig. 4.   Fig. 5.

Two Photographs of the Same Patient.

This man shows in a marked degree the backward position in which the head is often thrown in severe cases.
In this case, which is one of great severity, the head is held obliquely as well.   Note the way
in which the cap has been pulled down over the eyes to keep the light out.

jump up and down. Lateral movement is rarely complained of. In a few cases the movements of the objects appear to be entirely due to head tremor, the eyes remaining relatively steady.

Headache. Most men complain of occipital headache, but pain across the temples and in the eyes is common. ' My eyes are like a ball of fire and feel as if they would burst.' The headache often comes on at night-time and keeps the patient awake. It is increased by exertion, stooping, or bright sunlight. One of the most marked features of the disease is the persistence of severe headache even when no other signs or symptoms exist and when the miner has been out of the pit for years. It is probable that these persistent headaches are due to the development of a psycho-neurosis.

Giddiness. Loss of sight, headache, and giddiness form a triad of symptoms which are rarely absent and which develop concurrently. Giddiness is increased by exertion, stooping, or sudden turning movements. In severe cases the man is ataxic and unable to get about without help.

Photophobia. Although not present in every case, photophobia is a common and distressing symptom. It is almost always associated with lid-spasm.

To obtain relief the men wear their caps over their eyes or use dark glasses.

Mental Symptoms. It is difficult to obtain a clear history from patients without asking leading questions. There is a mental dullness and answers are often monosyllabic.

' What is the matter with you ? '

' Eyes.'

' Yes, but what do you complain of ? '

' Eye-stagmus.'

Men who eventually read the 6/9 line will hesitate over the 6/24 line. Restlessness and sleeplessness at night are very common, fits of depression and outbreaks of crying common. In the later stages of the disease the man may show the symptoms and signs of neurasthenia or a neurosis with constant headache, sleeplessness, anxiety, dreams, marked mental depression, loss of memory, generalized tremors, rapid pulse, and other changes.

This subject is dealt with later in a Report by Dr. Rivers.

B. Physical Signs.

General. The disease can often be recognized at a glance by the backward or oblique inclination of the head, hesitating gait, shading of the eyes, and lack of facial expression. On closer examination a head tremor may be felt and a rotatory oscillation of the eyeballs seen on asking the patient to look up.

Oscillation of the Eyes. Oscillation of the eyes may be obvious or brought about by asking a patient to fix a near point, elevate the eyes, or stoop rapidly. The oscillations are elliptical and generally rotatory, regular, and synchronous in both eyes. They are increased by exertion, stooping, elevation of the eyes, or confinement to a dark room, and are brought to a standstill by rest, covering the eyes, or asking the patient to look down.

The movements are often obscured by lid-spasm, rolling up of

the eyeballs under cover of the upper eyelids, strong convergence see (Fig. 23), lateral fixation, and in many cases by irregular semi-voluntary slow movements of the eyes. Oscillation of the eyes is always present in one stage or other of the disease, but its detection is often very difficult and may require repeated examinations after exercise and confinement in the dark.

Rate of movement.—The rate varies from 100 to 350 oscillations a minute, but occasionally even greater frequency may be observed. Ohm (31) gives the rate as 150–400, but in 70 per cent. of his cases the rate was between 250 and 350. Stassen's figures are 90–360.

Extent of excursion.—The excursion varies greatly, being of small amplitude when the rate is great, and coarser when the oscillations are about 100.

The degree of elevation of the eyes above the horizontal level required to bring out the oscillation has been taken as a measure of the severity of the disease. The test has a certain value, but too great reliance must not be placed upon it, as incapacity depends on a large number of factors, of which oscillation of the eyes is only one.

Ohm, who has paid great attention to the registration of these ocular movements, says (32, p. 36): 'Nystagmus appears in a variety of forms, perpendicular, horizontal, oblique, rotatory, circular, and so on, either equally marked or different in both eyes, now pendulum like, now jerky (ruckförmig), oftenest seen with elevated, seldom with depressed visual regard, more marked on either the right or left field of vision. This bewildering array of phenomena is the result of a disturbance of the vestibular control of the eye muscles.' The oscillations are constant over long periods, synchronous in both eyes, relieved by light and aggravated by darkness. The nystagmus of miners resembles the pendulum nystagmus of children, the tremor of old age, and the nystagmus produced experimentally in animals by darkness. Stassen (46, p. 110), after studying the tracings of the different varieties of nystagmus, comes to the following conclusions:—

(1) There exists a fundamental difference between the ocular tracings shown by miners' nystagmus and the nystagmus resulting from labyrinthine disturbance.

(2) The nystagmus of miners is undulatory.

Coppez (4) holds that most forms of congenital nystagmus and all varieties of labyrinthine nystagmus are completely different from the nystagmus of miners.

Lid-spasm. Lid-spasm was present in 501 cases out of 2,000 and marked in 75. Lid-spasm is involuntary, persistent, synchronous, and often associated with a fibrillary twitching of the eyelids. When marked it greatly interferes with the examination of the eyes. It is associated with photophobia and appears to be to a certain extent antagonistic to oscillation of the eyes. By many colliers it is considered to be the result of the involuntary blinking which protects the eyes from flying particles of coal. This view is apparently held by Stassen, who describes it as a reflex protective movement (46, p. 147). Ohm regards the spasm as compensatory to the ocular movements. The writer's view is that

it is the result of the reaction of the body to the disease, and a protection against photophobia.

Head Tremor. Head tremor was present in 628 cases out of 2,000 and marked in 103. Head tremor is a constant sign of the disease, and when associated with resistance to backward movement may be regarded as characteristic. These signs are often the last to disappear, and are of great value in estimating the genuineness of a case in which all oscillation of the eyes has disappeared. In severe cases the head tremor is accompanied by tremors of the shoulders and arms. The tremors of alcohol and old age resemble this condition and may give rise to error in diagnosis. One of the best ways of bringing out this head tremor, and incidentally nystagmus, is to flex the head strongly and ask the patient to look up. The observer will feel a marked sense of head resistance and a fine tremor which rapidly becomes coarser.

Among other signs may be mentioned strong convergence and the opening of the mouth when the patient is asked to look up.

In the later stages of the disease the signs resemble those of a neurasthenia or neurosis, and the clinical picture shows infinite variety.

C. Course of the Disease.

The disease may remain latent for years or pass gradually into the manifest form. Even where the man is aware of his condition he may be able to continue working for years and pass into a state of equilibrium in which he is able to ignore the ocular movements. This condition is well recognized, and it has been suggested by Norman that the workman should struggle on after onset of symptoms in order to reach this state.

The course of the disease may be divided into the three stages of onset, complete incapacity, and recovery. The onset is generally gradual, and in the present series of cases an average period of 14.5 months elapsed between the first symptom and failure. In some cases, however, the onset is sudden and the man may have worked up to a given date without any inconvenience. This sudden onset is frequent after accident or ill health.

Total Incapacity. Some men after failure are able to work at once on the surface, but most require complete rest. In this stage of the disease the symptoms of headache, giddiness, and night-blindness are marked. Total incapacity may last from one to twelve months, after which time the man is able to do almost any surface work. A few of the most marked cases never completely recover, and remain permanently unable to produce work of any marketable value to the colliery owner.

Recovery. In this stage the man is able to do any work on the surface, and the sooner he starts this work the better the prognosis. This stage may last twelve months, but here again will be found men who make no further progress and remain permanently unfitted for underground work.

In the later stages of this period the man is able to work underground as a labourer or assistant repairer. Complete recovery

with return to work at the coal face is frequent, but relapse is common, and with each failure the outlook for complete recovery is less likely.

While the general description given above is correct for the ordinary case, the clinical pictures presented by the more marked cases are of the most varied type. In these cases the symptoms and signs vary with the reaction of the individual against the disease. Three types of the disease, the atonic, the spastic, and the psychic, can be recognized, but they run into one another and cannot be sharply defined. In the 'atonic' form the reaction of the patient is feeble and the chief symptoms and signs are: loss of sight, headache, giddiness, and oscillation of the eyes. In the 'spastic' form the reaction of the patient is marked, and lid-spasm, photophobia, head tremor, and headache are marked. Oscillation is less marked and often very hard to detect. In the third or 'psychic' form the development of a neurosis or psycho-neurosis with generalized tremors, palpitation, sweating, headache, and sleeplessness presents a picture resembling traumatic neurasthenia or the war strain of soldiers. These three types of the disease resemble the retinal, clonic, and psychic division made by Stassen (46, p. 84).

V.   Aetiological Factors.

A.   Attention paid to the Disease.

The great variations in incidence cannot be explained unless the influence of the attention paid to the disease is taken into account. The inclusion of miners' nystagmus in the W. C. A. of 1906 has certainly brought the disease into prominence. The disease is earliest recognized and most prevalent in the large centres of the industry, and less marked in outlying districts and isolated pits— for example: the incidence of certified cases in a large anthracite colliery in north-west Glamorganshire was practically negligible up to 1911 ; in 1919 the incidence was 0·51 per cent., while that of the whole of Glamorganshire was 0·35. The conditions of work were unchanged, but the knowledge of the disease had grown. The low incidence in the extreme west of the Welsh coalfield is due partly to the use of naked lights, but also to the lack of knowledge of the disease. In Shropshire and North Wales, small isolated coalfields, the incidence is low. In certain districts of England, notably York-shire and the Midlands, where the men and men's officials are keenly alive to the benefits to which they are legally entitled, the incidence is high.

Mr. Gillhespy, general manager of the Yorkshire Coal Owners' Mutual Indemnity Company, in his evidence before the Workmen's Compensation Committee in 1919, stated that an examination of a typical Yorkshire pit, employing 2,000 men, by Dr. Moxon showed that 25–38 per cent. (according to the grade of employment) of all men over the age of 21 working underground showed oscilla-tion of the eyes. Every one of these men could obtain a certifying surgeon's certificate and be legally disabled. In the great majority of cases the oscillation of the eyes produces no incapacity and should

not in itself entitle the man to compensation. Mr. Gillhespy (64) says that the result of the scheduling of the disease has been to increase the incidence from 30 in 1907 to 515 in 1918.

Question 5677 : ' There is one cause and one cause only—that is the chief thing—to account for this difference, and that is compensation.'

Question 5715 : ' It follows from that, that the difference in numbers must of necessity import the element of ungenuineness ?—To this extent, that they were legally genuinely disabled, but not in fact disabled. Also, unless the law makes the definite assumption that men with nystagmus can work, and must work, on the surface at the end of say six months, and unless the law definitely fixes the reduction to be enforced in the compensation, employers will be helpless, as a man with nystagmus can always allege that he is unable to work even on the surface, and to ask an employer to prove a man's fitness is simply asking an employer to attempt the impossible. Now the next paragraph is why I am here. Looking at the subject from the point of view of the men themselves, up to 1907 30 men per annum were disabled. Now 515 men are disabled. The 485 additional men (515 less 30) themselves sacrifice one-half the wages they might be earning. The men, themselves, in the aggregate are thus unquestionably much worse off than if nystagmus had never been added to the Schedule of the Workmen's Compensation Act. If the deduction is also made that the disability in each case has grown as much as the number of claims has grown, the amount lost by the men each year, in wages, is huge. That is why I have come here, Sir. I want to show you this, that nystagmus was put into the Schedule of the Act at the request of the men and for the benefit of the men.'

Mr. Gillhespy's facts are indisputable ; it is probable that 25 per cent. of all men over 21 working underground could obtain a certifying surgeon's certificate and be legally disabled. He has omitted, however, to take the psychic element of the disease into account, and his conclusions should be read in the light of Dr. Rivers's report : ' It is quite certain that compensation has not increased the prevalence of nystagmus in the strict sense. It is solely through its action upon the psychical and psychoneurotic aspects of the disorder that the increased frequency of disability has come about.' See p. 64.

Mr. W. P. Richardson (Durham), Representative of Colliery Firemen (M.L.C.) :
' The increase of the number of cases of nystagmus is probably more due to the new consciousness that men were suffering from it than to any real increase.'

In North Staffordshire several ironstone pits, worked with safety lamps on account of the presence of coal seams, were closed down in January 1921 owing to slackness of trade. In one pit employing 565 men 12 cases were certified in the fortnight after the pit had closed and 2 more cases, making 14 in all, in six weeks. There had been 7 cases certified in the preceding twelvemonth. The experience of other ironstone pits was the same, and 21 cases were certified in three weeks from pits which had been closed down.

After the coal stoppage of 1921 several collieries experienced difficulty in finding work for all their employees. In one colliery, employing 645 men underground, in which 3 cases had been certified in 1920, it was impossible to find work for 250 men when the pit restarted after the strike. Within six weeks 18 men, for whom it had been impossible to find work, were certified as disabled by nystagmus. Altogether 23 cases have been certified between July and November 20, 1921, but there has not been a single failure from among the men who returned to work when the pit started.

Number of men.	Cases of nystagmus July–November 1921.
250 men given notice	23
400 resumed work	0

One man, who had left the pit four years previously for defective sight (high degree of myopia), emboldened by the success of his fellow workmen, obtained a certificate of disablement by nystagmus. This certificate was, however, upset on appeal to the medical referee.

The statistics on which Table III is based were obtained through the courtesy of the chief mutual indemnity societies in England and Wales.

TABLE III. *Returns from Mutual Indemnity Societies for the year* 1920.

District.	Percentage incidence of nystagmus.	Cases settled.	Cost per case in year. £	Percentage of cases working	
				U.G.	Surface.
A	0.68	0	32	10·4	68·8
B	0·54	0	34	29·1	42·6
C	1·40	2	47	not available	
D	0·58	12	32	49·5	21·0
E	1·88	169	112	3·0	33.5
F	1·14	5	89	28 per cent. receive no compensation	
G	0·80	10	30	74 per cent. at work	
United Kingdom.	0·72				

The high incidence, the low rate of return to work, and the high cost of the individual cases in district E appear to be directly related to the policy of settlement. In this district the men and the men's leaders are keenly alive to the advantages of lump sum payments. It is quite common, however, for the men to return to work underground after a lump sum settlement has been made. The geological conditions, methods of work, and life-history of the cases show little difference from similar conditions in neighbouring coalfields.

Incidence of the Disease in a Monmouthshire Valley. An investigation was made of the high incidence rate at an important group of collieries in Monmouthshire. See Table IV. Every facility was offered by the company, through the general colliery manager. Most of the company's pits are situated in the same valley, the older pits near the outcrop at the top and the

more modern pits down the valley. The geological conditions, seams worked, and methods of work differ in no way from those of neighbouring valleys in which the incidence rate is much less.

Full statistics were obtained, fifty cases examined, and photometric observation made in two pits.

The average illumination at the coal face in pit 48, which is one of the hottest and dustiest pits belonging to the company, was just under $\frac{1}{100}$ of a foot-candle. Surface brightness of coal 7·5. Both these readings are low. The average illumination at the coal face in pit 45 was 0·017 of a foot-candle. Surface brightness 8·5. These readings are also low. The longwall system is employed and there is very little holing.

Cases examined: Of the 50 men examined at least 8 men were not suffering from miners' nystagmus and 6 cases were doubtful. That is to say, at least 16 per cent. and possibly over 20 per cent. of all cases were wrongly diagnosed. These figures show a great readiness on the part of the men to give up work and a tendency to attribute any trouble to nystagmus. The return to work rate is high, and the general colliery manager in his evidence before the Miners' Lamp Committee said, ' Over a period of 3 or 4 years the records of these collieries (5,895 employed) show that 292 men suffering more or less from nystagmus were able to keep at work, and 120 who were on compensation for the complaint to return to work, with electric instead of flame lamps '.

This high return to work rate suggests that the cases were not severe, and it is also possible that many of the 292 men who kept on working when given an electric lamp made their eye trouble a pretext to obtain ' prior delivery ' when the electric lamps were

TABLE IV.

No.	Character of pit. Temp.	Dusty.	Method of working.	Holing.	Lamps.	Seams.	Ventilation. c. ft. per min. Ret.	Average incidence nystagmus 4 years.
42	Mod.	No	Longwall	None	Oil	2–3 ft.	27,560	1·80
44	Hot	Yes	,,	,,	{ $\frac{1}{3}$ Oil $\frac{2}{3}$ Elec. }	5 ft.	97,880	1·65
45	Hot	Yes	,,	,,	,,	3 ft.	53,860	1·10
46 47	Hot	Yes	,,	,,	Electric	3 ft.	{ 84,560 69,050 }	1·80 1·60
48 49	Hot	Yes	,,	,,	{ Chiefly Oil }	3–5 ft.	{ 69,050 93,660 }	1·30 1·80
50 51	Warm	Yes	,,	,,	{ $\frac{2}{3}$ Oil $\frac{1}{3}$ Elec. }	3–5 ft.	{ 116,250 93,700 }	0·50
53	Warm	Yes	,,	,,	Electric	5 ft.	142,250	0·67
20	Warm	Yes	,,	,,	,,	4–5 ft.	306,000	0·30

Pit 42. Very old pit, now closed down and men distributed to pits 44 and 45 chiefly. Ventilation in this pit not so good as the others.

Pits 50, 51. These pits are situated in another valley, and men are drawn from a different source.

Pits 53, 20. New modern deep pits, electric lamps always in use. New labour used to a certain extent.

The migration of men is from above down.

Pits increase in depth from above down.

Illumination. There has been a gradual introduction of electric lamps, and in 1921 3,665 oil lamps and 6,175 electric lamps were in use

Absentee rate from work, 12 per cent.

Accident claims show a fall from 15 per cent. in 1916 to 11·6 per cent. in 1920.

being introduced. The miners' leaders in the district are described as very keen and able men and greatly interested in the subject of miners' nystagmus.

The general result of the investigation is to suggest that, although the illumination is low, the chief factor is the attention paid to the disease in the valley. It is interesting to note that the incidence in pits 50 and 51, which are outside the valley (although
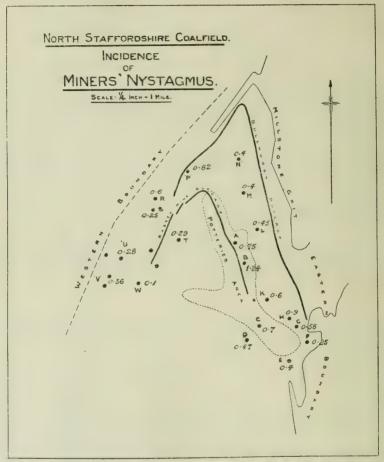
FIG. 6. Incidence of miners' nystagmus for the four years 1917–20 inclusive in the North Staffordshire Coalfield. The dotted area represents the five towns of the Potteries. Note high incidence in town area and low incidence in the western part of the coalfield, where the pits are very 'gassy'.

the workings extend into the valley), is much lower than the other pits. It is not fair to compare the modern deep pits, which have been largely manned by green labour, with the older collieries.

Incidence of the Disease in North Staffordshire. In this area the incidence of the disease is high. The mining conditions resemble those of neighbouring coalfields, and the present investigation has so far failed to discover any reason for the high frequency

Fig. 7.—Bottom Holing in a Seam 4½ ft. Thick.

The collier is kneeling at his work and is holding his body a little inclined. The direction of vision is downwards. The light, a small open oil lamp, is placed on the ground close to the area of coal face worked. This photograph shows the method of holing usually employed in seams over 3 ft. thick

These photographs were taken on the surface. The man posed himself, and his position was not altered. Notice the direction of visual regard.

FIG. 8.—THE SEMI-RECLINING POSITION.

FIG. 9.—THE FULL RECLINING POSITION.

The lower leg is drawn up a little and the lower shoulder rests on a pad of coal dust.

beyond the attention paid to the disease locally. Fig. 6 shows the local variation in incidence, and it is interesting to note that the rate is lower in the mining villages than in the town area. The western area, where the pits are gassy and where it is the custom to keep the gob flooded with gas to prevent fires, shows the lowest rate of incidence.

B. Occupation.

Although every class of underground worker is affected, 81·5 per cent. of all cases come from the coal face. The normal proportion of coal-face workers to men employed in the pit is 60 per cent.

TABLE V. *Giving an Analysis of the Occupation in 2,000 Cases.*

Colliers	1,510
Loaders	118
Timbermen and repairers	221
Hauliers	59
Rippers and hard ground men . . .	41
Labourers	21
Under officials	20
Various	10

Under the term various are included three drivers of underground motors, ostler, mason, and shot-firer. The earlier authorities thought that the disease was almost confined to coal-getters, but it is now acknowledged that all classes of men are affected.

C. Method of Work.

It is important to realize that the coal-getter is a highly skilled workman and that the blows which he makes with his pick are all accurately placed. In the process of holing, the operation on which blame has been placed, the collier kneeling or reclining on his side undercuts the coal or shale under the coal for a varying distance. In ' stent ' holing the coal is undercut to a distance of four or five feet. Another operation consists in ' cleaning the top coal ', or top holing when the coal at or slightly above the level of the eyes is being trimmed preparatory to the freeing of the coal at the buttock. It has been alleged that the operation of holing necessitates a constant upward direction of gaze. This is true to a certain extent for top holing, but in bottom holing the direction of the gaze is forwards or downwards. For a full discussion see Llewellyn (22, pp. 42–5). The position which the collier assumes is one which a novice would find awkward and uncomfortable, but it is one to which the man has been always accustomed and one which causes him no inconvenience.

Holing is common in the thin seams of the candle pits and nystagmus rare, while in the thicker seams of the safety lamp pits holing is less frequently carried out and nystagmus common. (See Fig. 20.)

The work of the timbermen and repairers is also of a skilled nature, and some of the timbering would not disgrace a carpenter. Their work is often carried out under conditions of great difficulty, especially when large falls in the roof have to be

supported with timber. This work has to be carried out at great speed, and owing to difficulty of ventilation and poor light obtained is of a strenuous nature.

It is, then, the skilled workmen, the men who have to use their eyes most, who are oftenest affected. This is in agreement with Stassen's (46, p. 66) conclusions that all classes of workmen are attacked, but that the disease most frequently attacks those workmen who use their eyes most—the hewers, the firemen, and the timbermen.

In the present series of cases the number of firemen who have failed is small, but this may be due to the regulation under which they submit periodically to tests of eyesight. Stassen also found nystagmus more common in the night-shift workers. In the United Kingdom most of the coal-getting is done in the day shift and most cases have come from these workers.

Table VI gives the amount of holing carried out by the colliers and men who had acted as colliers in the present series of cases.

TABLE VI. *Holing.* 1,510 *Colliers.*

Much holing	. . . . . .	466
Some holing	. . . . . .	484
Little or no holing	. . . .	560

Taking the whole of the 2,000 cases into consideration, over 50 per cent. had done little or no holing.

D. COLLIERY FACTORS.
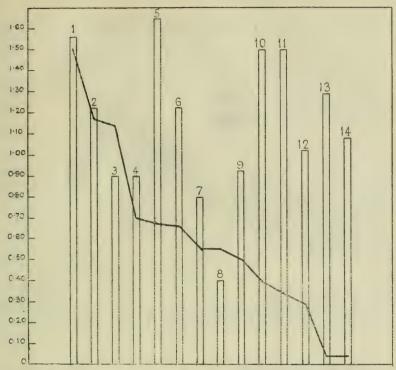
(1) *Age of Colliery.* In South Wales the older pits at the heads of the valleys, e.g. those at Rhymney, Tredegar, Merthyr, and Aberdare, and those near Risca in the south-eastern outcrop, show a higher rate of incidence than the deeper and more modern pits in the centre of the coal basin. The high incidence probably results from the employment of older patterns of lamps, older methods of ventilation, and older men—the average age of the workmen employed in old pits is usually high. In an investigation of an old colliery near Aberdare, showing a high incidence, all these factors were found, the men employed were over the average age, the labour turnover small, and the illumination at the coal face poor. (See pit C, p. 35.)

(2) *Depth of Colliery.* Nystagmus is held to be more prevalent in deep mines, and the increase of nystagmus is attributed to the working of the deeper seams. This belief is not borne out by facts. In North Staffordshire there are two adjoining collieries : one over 3,000 feet deep, hot and dusty ; the other 700 feet deep, in which the nystagmus incidence rate for the last ten years has been as 112 is to 100.

A graph has been prepared correlating the incidence rates of the various districts with the average depths of the pits concerned.

Only in North Staffordshire and Yorkshire is there any apparent connexion between the two sets of figures.

GRAPH II. Showing percentage of miners' nystagmus and depth of mine in thousands of feet in the districts : (1 North Staffordshire, (2) Yorkshire, (3) Cumberland, (4) Cannock Chase, (5) South Wales, (6) Notts, (7) Durham, (8) Northumberland, (9) Derby, (10) Warwick, (11) Lancashire, (12) North Wales, (13) Bristol, (14) Somerset. The parallelograms show the depth, and the curve the percentage of nystagmus.

(3) *Thickness of Seam.* There does not appear to be any definite connexion between the thickness of the seams and the incidence rate. There are fewer men working in the thin seams, and the figures given in the table do not represent the relative proportion of cases to men employed. It may be argued that a holer in a thick seam is really working in what may be considered a thin seam when he lies beneath the coal he has undercut. In the thin house-coal seams nystagmus is rare, in thick steam-coal seams nystagmus is common.

TABLE VII. *Showing Thickness of Seam in which* 1,613 *Coal-face Men worked.*

Thickness of seam.	No. of cases of nystagmus.
Less than 2 feet	1
2–3 feet	65
3–4 ,,	221
4–5 ,,	328
5–6 ,,	347
6 feet and over	650
	1,613

Figs. 10 and 11.   Map of South Wales Coal Field.
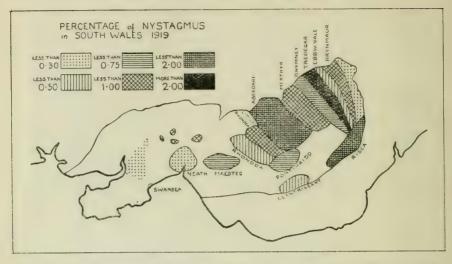
Fig. 10.   Showing percentage of all cases of miners' nystagmus in South Wales in 1919 arranged in districts which correspond generally to the valley formations.
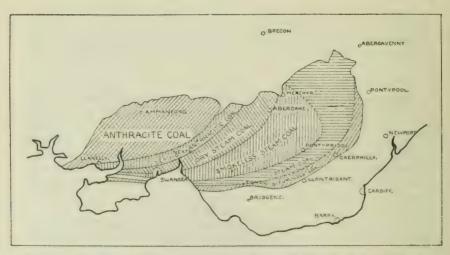
Fig. 11.   Showing the class of coal found in South Wales and the gradual transition from the bituminous coal in the east to the anthracite coal in the west.

(4) *Class of Coal.*   It has been suggested by Coulter (5) and others that the disease is more prevalent in the semi-bituminous areas and less frequent in the anthracite districts.   Taking South Wales as an

example, the coal from east to west gradually loses its bituminous character. The incidence of the disease does not correspond to this change, as will be seen from a study of the two maps of the South Wales Coalfield (Figs. 10 and 11).   Several anthracite collieries north of Swansea show a high rate of incidence, some of the eastern areas a low rate, while in between are found many variations. See also p. 22.

E. Illumination.

(1) *Clinical.*

Miners' nystagmus is found in all classes of coal mines, including ironstone mines where on account of the presence of thin coal seams safety lamps are employed.   In metalliferous mines the disease is unknown, but Stassen has found nystagmus, causing no incapacity, on examination of zinc miners (46, p. 50).

The disease is very uncommon in the purely naked-light districts of Somerset and the Forest of Dean, and less marked in Scotland, where one-third only of the workers use safety lamps, than in those coalfields using safety lamps universally.

Mr. Mark Brand, Scotland (M.L.C.):
Nystagmus is practically unknown in Scotch mines—where open lights are used.   This is attributable to the better light given by these lamps.   There are a few cases, probably in men coming from safety lamp pits.

Mr. Jas Borland, Ayrshire (M L.C.):

Table giving number of men employed and cases of nystagmus in Ayrshire.

	Men employed.	Cases of nystagmus.
Whole district	10,966	11
Annbank, Auchincruive, and Tofts *	1,439	10

* The pits in this district are largely worked by means of safety lamps.

Mr. J. Strachan, Secretary to the Federation of Colliery Undermanagers (M.L.C.):
A good light will practically abolish miners' nystagmus, which is a disease unknown in open-light pits.   Worked twenty years in open-light pits and never saw a case there.   Sufferers in a safety lamp pit sometimes go to an open-light pit—'and soon get all right'.

Nystagmus is common in Belgium, France, and Germany, where safety lamps are almost universally used.   In America, where open lights and electric cap lamps are used, the disease is very uncommon. In Japan, where the general method of lighting is by means of acetylene lamps, the disease is rare.

Examination of Workmen.   Court (6) in an examination of 1,169 men found 34 per cent. affected in safety light pits and 5·6 in candle pits.   Nieden (27) in an examination of 11,145 men found 4·7 per cent. in safety lamp pits, 1·6 in pits using lamps and candles, and 0·065 in candle pits.   Stassen (46, p. 183) in an examination of over 11,000 men found from 4·5–6 per cent. of serious cases in safety lamp pits and 1·3 per cent. in candle pits.   No grave cases were found in candle pits.

The present investigation has brought out statistical confirmation of these results.

TABLE VIII. *Incidence of Miners' Nystagmus in* 1919.

District.	Rate per 100 underground workmen.	Percentage of safety lamps in use.
Bristol and Forest of Dean	0·03	nil
Scotland	0·08	33
England and Wales	0·28	95 *
South Wales		
Candle pits	0.023	nil
Safety lamp pits	0·38	100

* Includes spare lamps.

Out of a series of 2,000 consecutive cases 1,951 had worked with safety lamps almost entirely, 35 with candles and safety lamps, and 14 with candles alone. It must be remembered that there are many more men working with lamps than with candles.

In a series of returns furnished by Mr. Binns of Derby, giving particulars of adjoining safety lamp and candle pits, the following remark by the manager occurred :—' It is significant that all the cases of nystagmus come from the open-light pit.' The pits were visited and an investigation brought out the following facts :—

Special Investigation of two adjoining Warwickshire Collieries.

(*a*) *Candle pit.* The pit was twenty years old, 220 yards deep, and the working places two miles in. The ventilation was good and the men used candles at the coal face. Men employed underground, 1,350 ; the floating percentage was estimated at 10 per cent. During the first seven years of the pit's life safety lamps were in general use throughout and consequently most of the men employed had worked with lamps.

From 1917–1920, both years inclusive, fourteen cases of miners' nystagmus had been certified. Of these men eleven had returned to work underground. The three remaining men, who were working on the surface, were examined.

One man had worked eighteen years with lamps and had had trouble during this time. The other two men, who had worked almost all their lives with candles, showed no oscillation of the eyes or other sign of nystagmus. They were both fit for pit work. One man, age 61, had evidently made up his mind he had done enough pit work.

The company paid no compensation as all the men were earning full wages. It is the custom of the management to find surface work at once, and the men generally returned to work below in twelve months. Two men had relapsed, but were at the time of the investigation at work below again. For illumination at coal face, see Pit A, p. 35.

(*b*) *Safety lamp pit.* This pit had only been opened two years, employed 350 men, nearly all of whom were new hands and therefore had not had time to develop the disease.

Miners' nystagmus is found in candle pits, but the attacks are generally slight. In a district where candle pits and lamp pits exist together it is quite common for men who have trouble with their eyes to change from a lamp pit to a candle pit ; these men often eventually fail, and unless great care is taken the blame is laid on the candle pit statistically.

In South Wales there are often two collieries working side by side, one drawing coal from the deep measures and using lamps, the

other working the house-coal seams with candles. An investigation of two such collieries brought out the following facts :—

	Men employed.	Cases of nystagmus.
Safety lamp pit	1,342	7
Candle pit	267	1*

The seams in the candle pit were from two to three feet thick and the coal was won by holing. The safety lamp pit seams were six feet thick and no holing was necessary. The manager states that there had not been a single case from the candle pit for the last seven or eight years until the man shown * above, coming from a neighbouring lamp pit where he had had trouble with his eyes, failed shortly after he had been set on. For similar comparisons see Llewellyn (22, p. 56).

The candle pit at Pleasley has attained a certain notoriety from its high incidence rate. Capt. P. Muschamp and Mr. Eustace Mitton in their evidence before the Miners' Lamp Committee both said that the incidence in this pit was greater than that of a neighbouring safety lamp colliery. Returns have been obtained from the collieries.

	Men employed.		Cases of nystagmus.	
	1912	1920	1912 *	1920
Safety lamp pit	1,500	1,330	31	19 or 1·43 per cent.
Candle pit	1,300	1,597	34	7 or 0·43 ,, ,,

* The figures for 1912 were for all cases on the books, for 1920 for cases arising in that year only.

A special visit was paid to these collieries in 1912 (22, pp. 75–7). It was found that a large amount of migration had taken place from the safety lamp pit. Of 13 cases examined six men had worked with lamps for years. The local doctor attributed the high rate in the candle pit to the 'unloading' of all men with eye trouble from the lamp pits to the candle pit. This, however, is not the complete explanation. In the candle pit the average illumination, on account of conditions of work, was much lower than the general illumination found in candle pits.

Nystagmus does occur in men who have worked all their lives with candles. These cases are, however, as a rule slight and the man is able to continue his work. If, however, the man's attention is called to his trouble by the failure of other men or by seeing the effect of the disease in men coming from a lamp pit, a comparatively mild or even latent attack may be converted into the manifest variety. The great reduction in the incidence rate in Pleasley is probably due to the greater care taken to prevent the employment of men from neighbouring safety lamp pits. The incidence is still high, as the disease is so to speak firmly established in the pit. It would be quite possible to 'infect' a pit, hitherto free from certified cases of nystagmus, by the introduction of a few bad nystagmus cases.

It is sometimes necessary to introduce lamps into pits where candles were in general use. This change is found very trying by the men, and they ask for increased rates of pay, even though they have had to supply their own candles while the lamps are an owner's cost.

C

In a colliery in North Staffordshire no cases of nystagmus had been certified until some years after the introduction of safety lamps. The incidence of the disease in this pit is now the average of the district. It is sometimes necessary to close a candle pit and distribute the men to neighbouring safety lamp pits. A small candle pit N. was shut down in North Staffordshire and the men sent to safety lamp pits belonging to the same company. No cases had been reported from the candle pit at the time of closure. Within twelve months eight men who had formerly worked at this pit failed on account of nystagmus. All these men said they could have continued in the candle pit, and six said they had never had any trouble until they started to work with lamps.

Case 1634. Worked with candles at N. for years; had a little trouble six years ago, but after four months' surface work returned to the pit and worked until his place was closed down. Sent to safety lamp pit, but failed after twelve months. Place was found for him again in the candle pit and he worked without trouble until the pit was finally closed. Sent again to the safety lamp pit, but was only able to continue for six months.

Case 1617. Age 68. 'I had no trouble when working with candles.' Failed after twelve months in safety lamp pit.

Case 1520. Age 59. This man had worked at N. for years and had never had any trouble. Failed at once when he started to work in the safety lamp pit. This man must have had nystagmus in the candle pit, but it caused him no inconvenience.

Colonel R. S. Williamson. Cannock Chase (M.L.C.), has heard of several cases among men who have always worked with naked lights, but there have been many more cases since safety lamps replaced open lights.

(2) *Photometric Data.*

Physical Considerations. The amount of light which reaches the retina is that reflected from the surface towards which vision is directed. This reflected light or surface brightness of any surface depends on two factors : the amount of incident light, which varies with the source of illumination, and the reflecting power of that surface—a constant factor.

A standard or international candle (1 c.p.) burns 120 grains of sperm every hour. The illumination given by a standard candle at the distance of one foot is one foot-candle. A more precise standard is the ten-candle pentane lamp, burning in pure air at standard pressure, and with 1 per cent. of aqueous vapour in the air.

The intensity of illumination varies inversely with the square of the distance from the source of light ; thus one candle at one foot, four candles at two feet, nine candles at three feet, all give equal illumination.

The illumination of a surface varies with the cosine of the angle of incidence of the light.

The International Illumination Commission, Paris, July 1921 (67), gave the following definitions :—

The *Unit of Luminous Intensity* (candle-power) is the *International Candle*, such as is derived from the agreement entered into between the three national standardizing laboratories in France, Great Britain, and the United States in 1909. This unit has been preserved since this date by means of electric incandescent lamps, in the laboratories which are charged with its preservation.

The *Practical Unit* of *Illumination* is the **Lux**, which is the illumination produced on the surface of a sphere of one metre radius by a uniform point-source of one international candle-power placed at its centre.

If one takes as the unit the length of one foot, the unit of illumination is the lumen per square foot, named 'foot-candle'. One foot-candle = 10·764 lux.

At the coal face the light which enters the miner's eye is the light reflected from the surface of the coal. It is very difficult to measure this light directly, but the amount of light falling on the working area can be readily measured by a portable photometer. The surface brightness of the coal can be measured at close range, and the combined measurements give the amount of reflected light. For example, if the light falling on the working area be 1/10 of a foot-candle, and the surface brightness of the coal 10, then the amount of reflected light will be 1/100 of a foot-candle (10/100 of 1/10).

Photometric readings. As a result of a large number of observations made up to 1912, Llewellyn found that the average illumination at the coal face in safety lamp pits was 0·018 of a foot-candle, and in candle pits 0·09.

Similar readings have been obtained in the present investigation. In some pits, however, the work is more detailed, and measurements have only been taken over the working area. These readings are higher. The introduction of the electric lamp has also improved the illumination. The measurements have all been taken with a Trotter photometer, and are expressed in foot-candles.

Photometric Readings at the Coal Face.

Candle pit (Warwickshire).

Pit A.
General illumination of coal face . . . 0·145 foot-candle
Collier bottom holing . . . . . 0·096 ,, ,,
,, squaring top 1st stall . . . . 0·130 ,, ,,
,, ,, 2nd ,, ... 0·208 ,, ,,
Candle used, 0·8 c.p.

Surface brightness
Dull coal 11
Bright coal . . . 12·5

Safety lamp pits (South Wales).

Pit B.
General illumination of coal face.
1st stall with very dirty electric lamp . . 0·01 foot-candle
2nd stall with clean oil lamp . . . 0·02 ,, ..
3rd stall with oil lamp . . . . . 0·01 ., ,,
Surface brightness of coal, 8–10.

Pit C. Average illumination at coal face, oil lamps used 0·01 ,, ,,

Pit D. Average illumination at coal face (4 stalls), oil lamps . . . . 0·009 ,, ,,
Surface brightness of coal, 7·5.

Pit E. Average illumination of coal face . . . 0·017 ,, ,,
Surface brightness of coal, 8·5.

Derbyshire. In these pits the men were employed at more special work, and the measurements taken are confined to the actual area at which the man was working or holing. The measurements are therefore higher than those of the

general illumination of the coal face. In the first pit the incidence of nystagmus was low, in the second high.

Pit **F.** *Electric lamps.*

Collier mid holing	0·06	foot-candle
Shovelling dirt from floor	0·01	,, ,,
Wedging coal down (2 lamps in use) . . .	0·07	,, ,,

Surface brightness of coal, 15.
The coal was very bright and covered with gypsum.

Pit **G.** *Oil lamps.*

Collier middle holing (4 stalls)	0·03	,, ,,

Surface brightness of coal, 8.

Nottinghamshire colliery.

Pit **H.** *Electric lamps.*

Collier getting coal, 1st stall	0·020	foot-candle
,, ,, 2nd ,, ...	0·033	,, ,,
,, ,, 3rd ,, ...	0·016*	,, ,,

* End of shift, lamp running down.

Staffordshire collieries.

Pit **I.** General illumination of coal face.

Electric lamps	0·009	foot-candle
Combustion-tube lamps	0·007	,, ,,

Pit **K.** *Oil lamps.*

Ripping top in crut	0·012	,, ,,
Loading dirt from floor	0·008	,, ,,
Thurling up bank	0·008	,, ,,
Collier in deep side cutting	0·007	,, ,,

Pit **L.** In this pit measurements were taken of working area only.

Collier winning coal 1st stall, oil lamps . .	0·028	,, ,,
,, ,, 2nd ,, ,, . .	0·020	,, ,,
,, ,, 3rd ,, ,, . .	0·020	,, ,,
,, ,, 4th ,, electric lamps .	0·035	,, ,,
,, ,, 5th ,, ,, . .	0·038	,, ,,
Collier bottom holing, 3 feet under . . .	0·017	,, ,,
Haulier spragging tram	0·030	,, ,,
,, pushing tub	0·012	,, ,,

Illumination at feet.

Fireman examining roof	0·023–0·010	,, ,,
Collier working coal-cutter	0·025	,, ,,

Pit **M.** *Combustion-tube lamp.*

Collier holing in thin seam	0·032	,, ,,
Examination of roof	0·080	,, ,,
General illumination of roadway 9 ft. 8 in. across at a distance of 4 ft. from man travelling with lamp in hand	0·008	,, ,,

(3) *General Considerations on Illumination.*

The illumination at the coal face depends on four factors :—
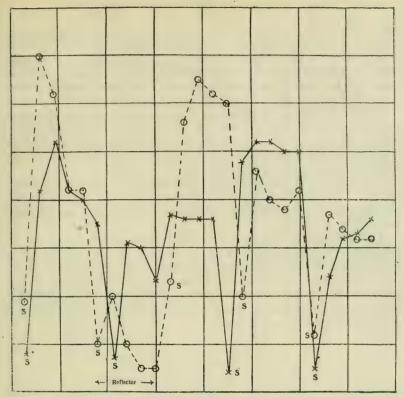
(1) The candle-power of the source of light used.
(2) The distance that light has to be placed from the working area.
(3) The surface brightness of the surroundings.
(4) The composition of the air at the coal face.

Candle-power of lamps used. Although there has been a great improvement of late years in the candle-power of the lamps used, it is only within the last year or so that a candle-power of two has been attained, and even these lamps are in the experimental stage

GRAPH III. Showing variation in candle-power of lamps and effects of standards,
S. Equidistant measurements taken at the circumference of a circle 2 ft. in radius
× 4 to give candle-power of lamp in a horizontal plane.
.... Hailwood's combustion lamp (clean).
--------Oldham electric lamp (after six hours use).
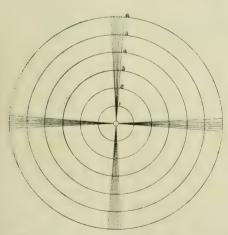
FIG. 12. Illumination data for Oldham lamp. Area of light in a 6 ft. radius circle, 109·39 sq. ft. Area of shadow in a 6 ft. radius circle, 8·71 sq. ft. Ratio of shadow to light, 1 : 11·98.
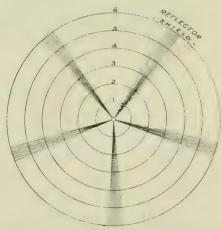
FIG. 13. Illumination data for Hailwood's lamp. Area of light in a 6 ft. radius circle, 97·15 sq. ft. Area of shadow in a 6 ft. radius circle, 15·95 sq. ft. Ratio of shadow to light, 1 : 6·09.

GRAPH III and Figs. 12 and 13 have been reproduced by permission from *The Illuminating Engineer*, vol. xiii. 3, p. 68.

only.   The candle-power claimed by the makers is rarely found in
practice (see Table IX), and even when found extends only over
a very limited area of the total field of illumination.   The Graph
and Figs. 12 and 13 show how the light is split up in the horizontal
plane by the standards and the great variation in candle-power
when the flame or filament is end on or broadside.

There is also a great variation in the vertical plane, and exten-
sive shadows are cast by the bonnet and reservoir of the lamp.
During the war years the lamp glasses supplied to the lamp makers
have been of an inferior quality and full of flaws which broke up
the field into blotches of irregular light.

The quality of the bulbs supplied has also been very unsatis-
factory.   In one set of photometric tests the same type of electric
cap lamp gave 1·4 candle-power with one set of bulbs, and 0·8 with
another !

The average candle-power of 531 lamps in actual use at six
large collieries was taken.   Half the lamps were examined clean or
freshly charged, and the others after they had been used in the pit
for a complete shift.   The oil lamps included Ackroyd and Best,
Protector, Hailwood's combustion-tube lamp, and Best's gauzeless
lamp; the electric lamps were the standard pattern Oldham and
Ceag, and the Oldham cap lamp.

TABLE IX.

	Number tested.	Candle-power. Clean.	After use.
Oil lamps	400	0·60	0·48
Electric lamps	131	0·80	0·58

It will be seen that the falling off in candle-power is more
marked in the case of the electric lamps.

The average candle-power of the lamps after a shift, and
the average percentage incidence of nystagmus for the last four
years in the six collieries, are shown in the table.

TABLE X.

Colliery.	Candle-power of lamps after use.	Percentage incidence of nystagmus.
A	0·66	0·36
B	0·58	0·40
C	0·50	0·47
D	0·40	0·70
E	0·39	0·75
*F	0·37	0·40

* Group of three pits, one of which is a stone pit.

Mr. Thomas Stott, Chorley (M.L.C.) :   The light-giving power of the present
lamps is totally inadequate even when they are kept in the best possible
conditions: as the day advances the efficiency of the light is considerably
reduced owing to glasses becoming dirty.   This bad light materially contributes
to nystagmus and possibly to other eye troubles, and to accidents.   Suffered
from nystagmus as a collier.   'It's all owing to the shortage of light.'

A large number of comparative tests have been made with electric cap lamps, standard electric lamps, combustion-tube lamps, and the ordinary pattern oil lamp. Some comparative readings will be given. The hand lamps were placed in position by the collier or workman and remained fixed, the cap lamps moved with the workman.

Colliery N.	Electric cap lamp.	Electric hand lamp.	Oil lamp.
Timberman at work			
Sawing a post	0·30	0·042	0.04
Wedging bar up	0.30	0.020	0·01
Shovelling dirt	0.20	0.020	0.02
Getting leg hole out	0·37	0·025	0.02
Collier at work			
Bottom holing	0.27	0.023	0·015
Top holing	0.60	0.100	0·080
Colliery O.			
Collier at work			
1st stall	0.13	0.020	0.013
2nd ,,	0.30	0.030	0.015
3rd ,,	0·30	0.016*	
* Battery running down.			
Colliery P.			
Collier in deep side cutting	0.30		0.007
Thurling up bank	0·37		0.008
Ripping	0.30		0.012
Holing in thin seam	0.15	0.06	0.070
Examination of roof	0.20	0.16	0·150
Illumination of roadway	0·014		0.008

The great difference in the readings results from the working of the laws of inverse squares and the cosine law (see definitions above). The cap lamp is much nearer the working area, and its rays fall at right angles and not obliquely as in the case of a stationary lamp. The readings show that the cap lamp often gives from ten to twenty times more illumination on the working area than an oil or electric lamp. The difference is so marked that it must be seen to be fully appreciated. A striking demonstration may be obtained if a collier with a cap lamp gets into position and turns his light on and off whilst another observer shields and uncovers the workman's lamp which had been left in place.

Care of Lamps.[1] Oil lamps of all descriptions, but especially those employing the combustion-tube principle, require regular attention from the miner. If a combustion-tube lamp is tilted, or hung up out of the perpendicular, smoking readily takes place, and the candle-power of the lamp will fall 50 or more per cent. The wick of all oil lamps requires frequent attention, and the outside of the lamp glass cleaning. The difference in candle-power between clean and dirty lamps is very considerable (see Table IX). Having no fear of 'losing the light' the miner takes greater liberties with the electric lamp than with the oil lamp, and the unorthodox employment of the case as an emergency tool stresses the terminals and plates of the battery, and reduces its life and light-giving properties. Men require education in the care of their lamps, and the plaint which a lamp manufacturer made at the

[1] See 'Report on Lamproom Organization and the Upkeep of Safety Lamps' recently issued by the Miners' Lamps Committee.

meeting of the Illuminating Engineers that the lamps were roughly used by the colliers, and that 'the miner appeared not to realize that the lamp was worth the few minutes' attention when he got to the coal face so as to get the fullest possible benefit' (59, p. 86), is fully justified. The miner should be taught to expend on his lamp the same care that the maker gives to its manufacture. Many colliery managers have made the mistake of entrusting the care of electric lamps to men who have had no experience, and although the lamp men have in most cases proved worthy of their trust, there is a period of transition in which the reputation of the new lamp suffers.

It is interesting to note that the lamp man in charge of Pit A (Tables IX, X) is a trained electrician who was especially appointed when electric lamps were introduced into the colliery. The lamps at this colliery gave the highest candle-power readings.

The Distance of the Source of Light from the Working Area. Distance is of great importance. There is a tendency for the workman to leave the lamp in one position too long, and men often work ten feet away from their lamp. The collier working in a deep side cutting hangs his lamp behind him, possibly at a distance of nine feet. His body and the swinging pick obstruct the light. The average light falling on the coal face may be less than 1/100th of a foot-candle! (see measurements, Pit P, p. 39). A cap lamp two feet from a working area would give twenty times as much light as a lamp of similar candle-power nine feet away. This does not finish the advantages of the cap lamp : there are no shadows, the light falls directly on the surface, and the man's body cannot get in the light.

Surface Brightness. Illumination in a confined space is very largely dependent upon reflection from the containing boundaries. An illustration given by Trotter (66, p. 24) will explain the great importance of this reflecting power : 'If lights amounting to 100 candle-power are placed in a room having walls, floor, and ceiling of a reflecting power of 80 per cent., one-fifth of the light will be absorbed and four-fifths reflected. This reflected light is for all intents and purposes a new light of 80 candle-power. . . . The total effective light in the room is therefore the same as if the walls and ceiling had been black, and 400 lamps of 1 candle-power each had been spread evenly over the walls, in addition to the original 100 candle-power.' This diffused reflecting power is practically absent at the coal face. The coal itself is black, the floor covered with coal and coal-dust, the roof, owing to the shadow cast by the bonnet of the lamp, is for the most part in darkness, while any little reflection from the gob is stopped by the back of the miner himself.

In the first report of the Departmental Committee on Lighting, 1915 (65), an account is given of experiments undertaken to determine the smallest amount of illumination which would enable a seamstress to work with black velvet, which absorbs 97 per cent. of all incident light, without experiencing discomfort. The amount found was four foot-candles. This figure should be contrasted with the average illumination of the coal face, 0·018–0·09 foot-candle.

Fig. 14.—Photograph of an Ackroyd and Best Lamp taken after an Eight-Hour Shift.

Fig. 15.—Photograph of the Same Lamp as in Fig. 14 taken Within a Few Minutes of the Last.

The lamp has been placed in a black box the same distance away from the camera as before. Exposure, development, and printing were all carried out under exactly similar conditions. Note the effect of absorption of light by the black surface. This absorption occurs underground.

Fig. 16.—Photograph of Roadway taken by the Light of Twelve Electric Lamps.

Fig. 17.—Photograph of the Same Roadway Whitewashed, Other Conditions Remaining Unchanged.

Fig. 18.—Blowing White Dust at Talk-o'-th'-Hill Colliery.

Fig. 19.—Road Surfaces coated with White Dust at Talk-o'-th'-Hill Colliery.

Figs. 18 and 19 are reproduced by the permission of the Council of the Institution of Mining Engineers from vol. lx, p. 370 of the *Transactions*.

It is now customary to whitewash the main roads for some distance from the pit bottom, and the compulsory introduction of stone dusting up to the coal face has increased the general illumination of the roadways in a marked manner.

The increased illumination of the roadways enables the miner to proceed to and from his work without delay and without the discomfort which follows the sudden plunge into the darkness of the workings. This toning down between the bright outside light and the darkness of the workings gives great relief to the miner. The saving of time which results from the miner being able to start off at once to the workings might easily amount to five to ten minutes a shift—a saving in a pit employing 1,000 men which would amount to nearly 150 shifts a week.

Photometric measurements taken in the Talk-o'-th'-Hill colliery show that the effect of stone dusting is to increase the illumination of the roadways from 100–400 per cent. Similar measurements at the Birchenwood colliery with Buxton limestone dust gave an increase of from 100—300. With the shale dust found in the pit the increase of illumination, although marked, is not so striking.

Surface brightness, chalk used at Talk	. . . .	100
,,	,,	Buxton limestone, white . .	57
,,	,,	Buxton limestone, pink . .	42
,,	,,	Birchenwood shale . . .	27–30

At the coal face, however, the collier works surrounded by non-reflecting surfaces. The surface brightness of coals varies considerably, from a dull uniform surface reflecting 5 per cent., to a coal covered with gypsum reflecting 16 per cent. of incident light. Elworthy (15, p. 688) thinks that pits which give the highest surface brightness readings have the lowest incidence of nystagmus, and gives some figures in support of his contention. Colliers working in deep side cuttings where they are surrounded by coal are especially liable to the disease.

In a Derbyshire pit with S.B. 16 the incidence of the disease was low, in a second Derbyshire pit with high incidence the S.B. was 8. In three South Wales collieries with S.B. 8, 8, and 5 the incidence rate was high. Measurements show that the surface brightness measurements do not appreciably differ between house and steam coals (22, p. 72).

Mr. Jas. Wilson, Durham (M.L.C.): Flame lamps are used, and there has only been one case in his colliery for the last twenty years. Cannot account for the small percentage. There is a large proportion of white roof in the top seams.
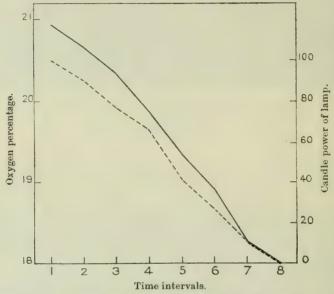
Composition of Air at Coal Face. The light of a safety lamp diminishes rapidly when the oxygen percentage of the air falls, and it has been shown (Haldane and Llewellyn, 1912, 17, see Graph IV) that the fall is roughly 35 per cent. to every 1 per cent. of oxygen. It is quite common in oxygen diminution for the lamp flame to remain large but without luminosity. The presence of CH_4 up to 4 per cent. increases the luminosity of the flame (21).

The presence of moisture also reduces the luminosity of the flame. In addition to changes in the composition of the air,

suspended coal dust not only clogs up the oil lamp but also absorbs light which would otherwise reach the coal face.

Quality of the Light. Elworthy and others have pointed out that the quality as well as the quantity of the light must be considered. Stassen (46, p. 222) speaks of the experiments by M. Henry in 1911, in fitting yellow glasses to the miners' lamps to combat glare. The lamps were appreciated by the men, but the experiment was stopped by the war and has apparently not been repeated. In this country a Joel Fors lamp fitted with a yellow tinted glass has been placed on the market. The makers claim that the reduction in light-giving properties is more than compensated for by the greater comfort obtained in the use of the lamp (59, pp. 215–16).

GRAPH IV. Showing how the candle-power of an oil safety lamp (broken line) falls when the oxygen percentage of the air (continuous line) is diminished. The candle-power at the beginning of test is taken as 100. Time period 1–8 is two hours.

Elworthy (16) suggests that incurable cases of nystagmus may be due to ultra-violet burns. He has analysed with the help of light filters the light given by a candle, oil lamp, and electric lamps, and found that the light from an electric lamp contains twice as many blue rays as that from a candle or oil lamp. These blue rays have an exhausting and irritating effect on the eye.

These experiments have been repeated in the course of this investigation. Elworthy's analysis has been confirmed, but his conclusions are not accepted. In practice blue rays never occur alone, and the amount given off by an electric miner's lamp is very small. This is also the opinion of Sir G. A. Berry: ' I doubt if any aetiological influence can be ascribed to the action of ultra-violet rays' (59, p. 97). Ferree and Rand (68), in a series of experiments on the eye with mantles of different composition, found that with

a saturation of green or red discomfort was produced. 'So trying was the experience that some time had elapsed before the eyes had regained their normal appearance and comfort.' These experiments were of course carried out with much greater intensity of illumination than that obtained from a miner's lamp.

Sir Josiah Court (M.L.C.) suggested the use of amber glasses for men suffering from nystagmus. He considered the ultra-violet rays to be harmful, and, unless the cost was prohibitive, would like an experiment made with euphos or Crookes's antiglare glass.

Fifty consecutive cases of miners' nystagmus, all of whom were off work, were exposed to a bright light which was at first unshaded and then screened with Wratten filters 86 B and 86 C, and aesculine (Kodak variant of euphos glass). The filters 86 B and 86 C are photometric yellow. Aesculine filter cuts off all ultra-violet rays. Of the 50 cases no relief was experienced by 34, and the men who experienced relief said the light was dimmer, but allowed no further improvement.

TABLE XI. *Fifty Cases of Miners' Nystagmus. Effect of screening Light with Wratten Filters.*

Cases.	Relieved.	Not improved.
Marked signs and symptoms	8	12
Slight signs and symptoms	7	12
Slight symptoms, no objective signs	1	10

The men showed no preference for the aesculine screen and preferred filter 86 B, which is of deeper tint, to 86 C.

Photometric measurements showed that the use of these screens reduced the illumination given by 10 to 20 per cent. In the table the unscreened light is taken as 100.

TABLE XII. *Showing the Reduction in Illumination from Use of Screens.*

	Unscreened light.	Aesculine.	86 B.	86 C.
Electric lamp	100	90	80	86
Electric cap lamp	100	91	83	91
Standard candle	100	93.5	90	90

The filters were chosen, aesculine because it cuts off all ultra-violet rays with little absorption of the rest of the spectrum, the 86 B and 86 C filters to bring the light more in line with a candle.

Glare. Although glare is generally associated with light of great intensity, in the low illumination of a coal mine any direct rays of light which fall into the eye produce inconvenience, amounting, in the case of the nystagmic worker, to discomfort and even pain. One of the objections made against the cap lamp is that the bright light annoys the men working alongside. Many colliers work in a reclining position with the lamp at their feet so that the light shines obliquely into their eyes. The effect of this

oblique illumination has been discussed by Parsons (65) (Royal London Ophthalmic Hospital Reports, vol. xix, Part 3). In oblique illumination the optic media are flooded with light, and with ' objects of relatively low brightness the presence of a surrounding field of relatively high brightness has the effect of lowering the capacity of vision both for detail and for brightness detail '. If a collier, for example, looks at the coal face he may receive less than 1/500 of a foot-candle reflected into his eye, and the light of a lamp of one candle-power shining obliquely into his eye is relatively high.

Mr. W. H. May, Workmen's Inspector (M.L.C.): Actual experience of some sufferers is that the white light of the electric lamp is better for their eyes than red light of flame lamp. It is not the users of a bright light that suffer, but those who have to look at it.

Mr. W. D. Woolley, Tredegar, Colliery General Manager (M.L.C.): Some workmen prefer the soft light of a flame lamp to the glare of an electric lamp; the latter is trying, and therefore probably harmful. The question of the surface of the seam affecting the eyes is of interest. Seams with dark shale roof and floor are certainly more trying than thicker ones with white clift roof.

Mr. McLoughlin of Brancepeth has submitted to the Mines Department suggestions for the elimination of nystagmus. He paints the pillars, lamp rings into which these pillars fit, and $\frac{2}{5}$ of the lamp glass with white enamel paint. Twelve men suffering from nystagmus when supplied with these lamps were able to continue work at the coal face.

The painting or frosting of part of the lamp glass has been in use for many years, and is of great service in preventing the annoyance caused to other workmen during the journey to the face.

Mr. Peasegood of Madeley has had 100 lamps painted in accordance with Mr. McLoughlin's instructions. The men at this colliery have always used a detachable metal shade while travelling to and from the coal face and do not like the shaded glass so well. If the metal shade gets in front from the swivelling of the lamp the man is conscious of the change at once; the painted glass is semitranslucent, and the man does not at first realize that the lamp has swung round, and gets into trouble with his fellow workmen. At the coal face the men do not like the glass shaded as it interferes with the all-round light. The lamps were painted with two coats of best white enamel, and it was found that the coating only lasted three days on the glass of the oil lamp and about a fortnight on the brass-work. The metal-work, pillars, and ring of the electric lamps were also treated, and the men say it improves the light. As a result of this test Mr. Peasegood has decided to enamel all the standards of his electric lamps, but to leave the lamp glass untouched. On the electric lamp the enamel lasts six weeks.

(4) *Results of Improved Illumination.*

A candle has been shown to possess great advantage over a safety lamp. It can be placed nearer the working area, gives an all-round light, remains constant throughout the shift, and casts no shadows. 'Taking all these factors into consideration, we may

say that the collier in a naked-light pit works in an illumination five to ten times as great as that obtaining in a safety lamp mine ' (22, p. 88). The discrepancy is not so great at the present time on account of the improvement in oil lamps and of the general introduction of electric lamps. In an investigation of the pits of the Rhymney Valley, in which all certified cases were examined and photometric readings taken at the coal face, the following results were obtained :—

TABLE XIII. *Rhymney Valley. Relation of Nystagmus to Illumination.*

	Relative percentage of nystagmus.	Average illumination at coal face in foot-candles.
Safety lamp pits	6·3	0·018 or 1
Candle pits	1·0	0·090 or 5

The occurrence of the two classes of pits, candle and safety lamp, has provided material for an experiment in illumination which has lasted for over 70 years. Improvement in illumination has not always been followed by a diminution of the disease. There has been since 1907, with the exception of the abnormal war years, a steady increase in the number of cases of miners' nystagmus. (See Graph I.) This increase is largely due to the attention called to the disease, to the increase of knowledge of the disease and resulting improvement of diagnosis, and to the doctrine almost universally taught that cases of nystagmus should not return to underground work even if they have recovered. This leads to an accumulation of long-standing cases (see p. 15). The disease, then, may be said to have increased in the same way as appendicitis has increased in the last 20 years. The benefit of increased illumination is not felt at once, as the disease is of gradual onset ; and it is undoubted that men on the point of failure are sometimes more troubled with the brightness of an electric lamp than relieved by the increased illumination which it gives. Many makers turned out inferior types of electric lamps which failed under the stress of pit work and brought general discredit on the industry. If a manager after introducing electric lamps does not obtain a diminution in the number of cases, it by no means follows that his venture has been a failure. His incidence rate instead of remaining stationary might have gone up.

The following table has been prepared from data supplied by Mr. Gillhespy, general manager of the Yorkshire Coal Owners Mutual Indemnity Society. Mr. Gillhespy attributes the fall in incidence in 1919 to the high wages paid, and not to any improvement in illumination. Electric lamps began to be used by the members in 1913, and by 1920 38 per cent. of all lamps used were electric.

Figures for the United Kingdom have been added.

TABLE XIV. *Yorkshire Coalfield. Relationship between
Illumination and Incidence of Miners' Nystagmus.*

Collieries.	Men employed.	Proportion of electric lamps in use.	Percentage incidence of nystagmus.		Percentage decrease.
			1913	1919	
Group I	39,831	Less than 25	0·61	0·52	15
,, II	.13,853	25–50	0·46	0·40	13
,, III	11,514	50–75	0·55	0·41	26
,. IV	19,555	Over 75	0·76	0·65	14
					Increase.
U.K.		Less than 25	0·26	0.28	8

Mr. Geo. Gibb, Scotland (M.L.C.): In collieries with about 750 safety lamps and 2.500 naked lights there were eight cases of nystagmus 5 or 6 years ago and only two now. The decrease is attributed to the use of electric instead of safety flame lamps.

Mr. Walter Hargreaves, West Yorkshire (M.L.C.): In Whitwood Collieries reported cases of nystagmus have increased since the installation of electric lamps in 1913. Does not attribute this increase to the use of electric lamps. The cases were probably latent and caused by the use of flame lamps. It is noteworthy that when wages increased in 1917, there was a drop in the number of cases. Before 1913 men who contracted nystagmus when working with flame lamps came back immediately and worked with electric lamps.

Mr. David Hannah, South Wales (M.L.C.): Cases have decreased owing to the use of electric lamps. There are cases where men could not work with oil lamps, but can do so with electric lamps. They have comparatively few cases, but his impression was that they occur more in naked-light pits where the flicker of the candle or the lamp is seen.

Mr. J. Robertson, South Derbyshire (M.L.C.): Nystagmus is on the increase in safety lamp pits ; but when electric lamps are used the conditions have been much improved. It is almost unknown in the candle pits. Figures of nystagmus cases would not be reliable owing to the effect of the W.C.A. in bringing more cases to notice.

Mr. Eustace Mitton, Mining Engineer (M.L.C.): In 1913, electric lamps were introduced at Kirkby, and later at Lowmoor, with a very marked reduction in the number of compensation cases.

4 years to 1914	0 97
,, 1918	0.38, a reduction of 60.80 per cent.

Elworthy (16, p. 80), whose figures have been supplemented by the courtesy of the company concerned, gives striking figures for Ebbw Vale. In the years 1909–11 the incidence rate was four times that of S. Wales. New fans were introduced and in 1914 electric lamps were installed.

TABLE XV. *Incidence of Miners' Nystagmus in South
Wales and Ebbw Vale.*

Year.	S. Wales.	Ebbw Vale.	Remarks.
1909 11	0·17	0·71	
1914		0·73	Ventilation improved and electric lamps introduced.
1915		0·22	
1916		0·17	
1917		0·12	
1918		0·12	
1919	0·28	0·10	Over 6,000 electric lamps in use.
1920	0·31	0.16	

FIG. 20.—COLLIERS USING CAP LAMPS IN A THIN SEAM.

This is the type of oil cap lamp used in the open light pits of South Wales
and Scotland. The colliers are engaged in bottom holing in
a thin seam Note direction of vision.
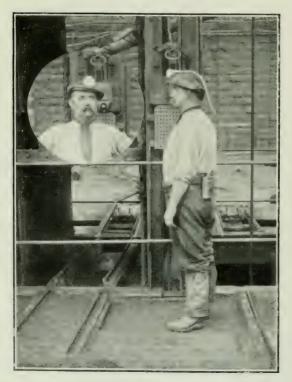
FIG. 21.—Workman wearing
an Electric Cap Lamp. The
accumulator is carried on the
belt and the cable is fastened
to the back of the cap. The
expanded bulb carrier is fitted
with a metal tongue which fits
into a strip of leather sewn on
to the front of the cap.

Inset shows front view of
lamp portion.

Most colliers wear the peak
of the cap behind.

With the introduction of improved ventilation and the use of electric lamps there has been a steady fall in the incidence of the disease, while neighbouring collieries, working under similar geological conditions, have shown a greatly increased incidence rate (see map S. Wales).

In N. Staffordshire, Mr. Johnson (58, p. 77) of the Mossfield Company introduced electric lamps into one of two collieries working the same seam under similar conditions. The incidence of the oil lamp pit was that of the district, while no cases developed for 6 years in the second pit, in which electric lamps were used at the face.

In two adjoining companies in S. Wales the yearly incidence for a period of 5 years in the pits of one company using oil lamps entirely was 0·57 ; in the pits of the second company, using nearly 50 per cent. of electric lamps, the incidence was 0·175.

The figures of Stassen, Nieden, and Court have already been quoted showing the increase in incidence in safety lamp pits.

Experimental evidence has been furnished by Ohm (31, p. 178). Ohm shut up three puppies and two kittens in a dark cellar, and found nystagmus in all the animals after an interval varying from 10–48 days. He was able to take tracings of the ocular movements, and found that they resembled those obtained from miners suffering from the disease. He also found experimentally that light has a calming influence on the oscillations and darkness an aggravating influence. This is in accordance with clinical experience that one of the best methods of bringing out oscillations is to shut the man up in a dark room for a time. An examination of pit ponies did not reveal nystagmus (20, p. 24).

It is also quite common for men to return to work with the help of an electric lamp after failure with oil lamps. The migration of men from safety lamp pits to candle pits when their eyes begin to be affected is quite common where the two classes of pits exist side by side.

Experiments in the use of electric cap lamps have been carried out in four collieries in N. Staffordshire. The improvement in illumination given by these lamps is dealt with above. It was difficult at first to overcome the natural conservatism of the miner, and in the first instances the lamps were only given to men working in the roadways. In this position they have proved successful in all classes of pits. In two deep and hot pits, where men work in pants and boots alone, the results have been up to the present disappointing. The miner, while greatly appreciating the increased light given, experienced great discomfort from the use of a cap and the dragging of the battery on the belt. In the first samples the cable was too short and movement of the head pulled the cap off. The men working alongside do not like the light shining into their eyes, but experience little trouble when they are themselves fitted with a cap lamp. Various mechanical defects have been brought out and rectified. In all 130 lamps have been used and the general conclusions are :

1. In pits of ordinary depth, where the men are able to wear caps in comfort, the lamps can be used with success at the coal

face. In hot pits, where the men work almost stripped, the lamps are not satisfactory.

2. The lamp can be used in the roadway in all classes of pits.
3. For special work, such as building a stopping, quick examination of the roof, and for hauliers, the lamp is superior to the ordinary pattern.
4. To obtain the best results the men should wear a special cap, the leather pit cap being perhaps the most satisfactory pattern.

Remarks by **Mr. Gardiner**, manager, Stafford Coal and Iron Co.:

Oldham Electric 'Cap' Lamp.

This type of lamp was first tried at these collieries about 12 months ago, and 27 lamps have been supplied. These lamps have been supplied in small batches at different times and each batch has had some detail alteration.

No reliable working costs have been obtained, but the cost of upkeep will probably be slightly in excess of the ordinary miner's type electric lamp.

The lamps have been well received by the men, but in the early batches the accumulators were of insufficient capacity and the light was poor at the end of the shift. This appears to have been overcome and in the later lamps a good light has been maintained throughout the shifts.

The lamps were issued to persons in different occupations and were found quite suitable. The only persons who did not appreciate them were one or two of the older men. The persons using the lamps found that both hands were left free, and that the light was concentrated on the spot they looked at. At first a slight discomfort is caused by the weight of the lamp on the head, but this soon disappears. The weight of the accumulator is scarcely felt, but in the case of a man stripped some discomfort would probably be caused by the chafing of the skin by the strap.

In the lamp-house the lamp is not so convenient to handle as the ordinary miner's type electric lamp. The bulk of the repairs necessary have been to the connexions at the lamp end of the flexible cable, and in all except the latest model these connexions are very inaccessible, causing the repair to take more time than it should. During the twelve months about 12 glasses have been broken almost without exception by the men allowing the lamp to strike against something whilst it was being carried in the hand on reaching the surface.

F. Mine Gases, by J. S. Haldane, M.D., F.R.S.

It has sometimes been suspected that the occurrence of nystagmus in coal miners might perhaps be connected with the gases abnormally present in the air. As, however, excess of CO_2 and deficiency of oxygen are met with to an even greater extent in pits worked with open lights than in pits worked with safety lamps, and nystagmus is practically absent in open-light pits, we can at once exclude excess of CO_2 or deficiency of oxygen as causes of nystagmus. The presence of firedamp in safety lamp pits has also to be considered.

As has been shown above, nystagmus is a disease connected with the use of safety lamps. But the use of safety lamps is associated with the presence of firedamp (methane) in air, and it might be argued that it is the firedamp, and not merely the bad light of the safety lamps, that causes the nystagmus. We must therefore consider this possibility.

All the known physiological effects of firedamp on men or animals can be explained as due to dilution of the oxygen of the air by the firedamp. In other words, all the known effect of breathing firedamp are due to want of oxygen. To obtain further certainty

on this point I made a mixture of 80 parts of almost pure firedamp from a blower with 20 parts of oxygen. On breathing this mixture for a few minutes I could not distinguish it from ordinary air. It produced no abnormal symptoms whatever. A mouse kept in it for a considerable time was also quite unaffected (69). Firedamp has thus no more physiological action than the nitrogen normally present in air, and it is impossible to attribute any physiological effects to the very small percentages (seldom over 1 per cent.) breathed by miners. Change of barometric pressure owing to residence at a few hundred feet above sea-level has a much greater effect in diluting the oxygen of the air.

Minute traces of carbon monoxide are also commonly present in mine air, since in the slow oxidation of coal at ordinary temperature a small quantity of carbon monoxide is formed. The proportion present is seldom over 0·005 per cent., however (70); and this proportion has no appreciable physiological action. There can be no doubt that every one of the very varied effects and after-effects of acute poisoning by carbon monoxide is due to the want of oxygen produced, owing to the fact that by combining with haemoglobin carbon monoxide interferes with the carriage of oxygen by the blood from the lungs to the tissues. Apart from its one very dangerous property of combining with haemoglobin, carbon monoxide is simply a physiologically indifferent gas like nitrogen or firedamp. This I showed experimentally by placing small warm-blooded animals in pure oxygen at two atmospheres pressure, and then forcing carbon monoxide into the air until the pressure was raised by an additional atmosphere, so that the haemoglobin was completely saturated with carbon monoxide. The animals remained unaffected in spite of the relatively enormous amount of carbon monoxide breathed by them (71), and this was evidently due to the fact that at two atmospheres pressure of oxygen their arterial blood contained sufficient oxygen in ordinary physical solution to enable them to dispense with the carriage of oxygen by haemoglobin. Animals which possess no haemoglobin were found to live perfectly well for weeks at a time in air containing 80 per cent. of carbon monoxide and 20 per cent. of oxygen.

An idea is prevalent that when carbon monoxide combines with haemoglobin the compound is stable, so that carbon monoxide, even if present in mere traces in the air, can go on accumulating to an indefinite extent in the blood, and may thus produce serious effects. This idea is entirely erroneous. There is a maximum limit to the extent to which the haemoglobin can become saturated with carbon monoxide when a given small percentage of the gas is present in the air breathed; and this maximum limit is far too low in the case of the air normally breathed by miners to cause any appreciable physiological effects. Moreover, any carbon monoxide absorbed is given off again when pure air is breathed.

Besides those already discussed, there are no other alterations in the gaseous constituents of ordinary mine air. We may therefore conclude with complete certainty that the abnormal constituents in ordinary mine air have nothing whatever to do with the production of miners' nystagmus.

Nystagmus is sometimes produced by acute poisoning with carbon monoxide, and cases are described in Glaister and Logan's book on *Gas Poisoning in Mining*, 1914. These cases had marked mental symptoms and the nystagmus itself is described as horizontal. On p. 262 is described 'a *remarkable oscillation of the eyeballs* following afterdamp poisoning, in which the movement is incessant and continued over a few days. This phenomenon has been noticed in a most exaggerated degree in cases of producer and illuminant gas poisoning.' It is certain that acute poisoning by carbon monoxide can produce a nystagmus or the irregular oscillation of the eyeballs described above, but these movements are not comparable with the oscillation of the eyes found in miners' nystagmus.

G. INFLUENCE OF ALCOHOL.

A distinction has been drawn between industrial and convivial drinking. The miner from the nature of his employment is shut off from industrial drinking, and only indulges after his day's work is done. Convivial drinking is much less harmful than industrial drinking, and although the incidence of *drunkenness* is very similar in mining districts and seaports the miner must be regarded as belonging to a comparatively sober branch of the community. The comparative mortality of males aged 25–65 from (a) alcoholism, (b) alcoholism and liver disease taken together, and (c) from all causes in the period 1910–12 is given below :

Occupation.	(a)	(b)	(c)
Coal-miner	3	13	727
Agriculturalist	3	11	474
Dock labourer	26	43	1,127
All males	7	23	790

(Taken from *Alcohol*, H.M. Stationery Office, 1919.)

Ohm considers alcoholism to be a predisposing factor in the disease. He has, however, found that large doses of alcohol lessen and even arrest the oscillations of the eyes, and says that in Germany the miners are aware of this calming influence of alcohol, and make use of it when they wish to be declared ' fit for work '.
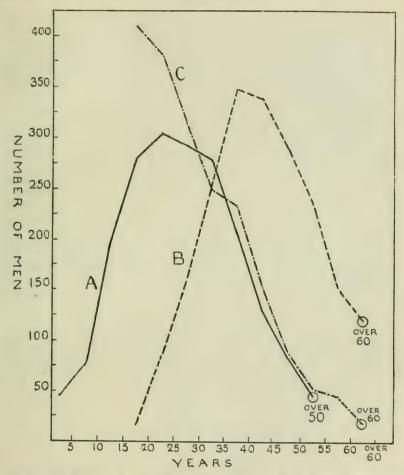
Ohm has given various alcohols with transient success. 'The effect begins in a few minutes, is most marked in half an hour, and passes off after an hour.'

From 1914, the scarcity, low alcohol content, and dearness of beer have led to an enforced condition of comparative temperance. During these years the incidence rate of the disease has not shown any decline. It is clear that alcohol can only be a secondary factor in the production of the disease. When the miner is in the acute or convalescent stage of the disease alcohol has a marked harmful influence, and a vicious circle is formed in which loss of work leads to drink and drink to prolongation of incapacity. Other things being equal the prognosis in an alcoholic is not so good as in an ordinary individual.

H. Personal Factors.

(1) *Age.*

In the present series of cases the average age of the workman at time of failure was 42·3 years, the average duration of underground life was 26 years, the youngest patient was 15, and the shortest

Graph V. Showing in quinquennial periods : Curve A. Number of years spent underground before onset of disease. Curve B. Age of workmen at time of onset of disease. Curve C. Age of 3,814 workmen employed in four steam-coal collieries. To read Curve C the number of men shown by the graph in each age group should be multiplied by two.

period of underground life was under 20 weeks. Ohm's youngest case was 16, and had worked 16 months in the pit. Stassen describes one case aged 13½ years, underground life 5 months, and a second case aged 14. Stassen says that after 55 the majority of hewers, timbermen, and crutters give up their work and ask for

lighter employment, and some, giving up heart, prefer to do no more work and demand pensions. At the other extreme may be quoted the following case :

J. G., aged 75. Underground from the age of 6! Has worked regularly at the coal face until disabled at present age by a severe injury to the eye. ' My eyes were always very strong and as a young man I could look at the sun.' No sign of nystagmus found.

(2) *Accident.*

Nystagmus frequently becomes manifest after injury to the cornea, and accident was the determining factor in the onset of the disease in 10 per cent. of the present series. The connexion in many cases is striking, and a man perfectly free from all symptoms of the disease presents a typical clinical picture shortly after an accident to his eye.

Injuries to the head, shock, and acute illnesses are frequently followed by the appearance of symptoms.

All these conditions probably act by aggravation of a previously existing latent stage which was causing no incapacity. It is not suggested that accident or ill health will bring out the disease in a man who had not been exposed for some time to the working conditions of a coal-mine. Many authorities, especially Dransart, have called attention to the frequency with which nystagmus follows an eye injury. Ohm, however, says it is wrong to say that accident causes nystagmus. After an examination of over 11,000 eye accidents he only found 150 cases of nystagmus, and of these 88 had nystagmus before (31, p. 283). Stassen also does not think there is any close connexion between accident and onset of the disease.

(3) *Hereditary Predisposition.*

Many authors suggest an hereditary predisposition, and the disease does appear to affect some families more than others. In the present series of cases several instances of two or more cases from the same family have occurred :

> Four brothers, all affected.
> Three brothers, all affected.
> Four brothers, two affected.
> Six brothers, three affected.
> Father and two sons.
> Several cases of two brothers.

The influence, if any, cannot be great and probably acts through the transmission of ocular defects.

Ohm (31, p. 7) says : ' From my incomplete observations members of families with deficient " light sense " are predisposed to nystagmus '; and again (31, p. 214) : ' Disturbances of dark adaptation and alcoholism have proved factors which predispose to nystagmus. Younger members of a family in which several cases have already appeared should be advised not to undertake pit work.'

TABLE XVIII. *Showing Degree of Error found.*

Up to 1 dioptre	.	.	.	.	.	257
1–2 ,,	.	.	.	.	.	339
2–3 ,,	.	.	.	.	.	122
3 and over	.	.	.	.	.	140
						——
						858

Although many men with normal vision suffer from the disease it is not unreasonable to suppose that the strain of working in a dim light is greater in men with defective vision.

(5) *Colouring.*

In the present series of cases there has been a preponderance of cases among the fair blue-eyed individuals.
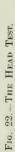
TABLE XIX. *Pigmentation, 2,000 Cases.*

Eyes.	Hair colour.			
	Fair.	Medium.	Dark.	
Blue	347	282	130	759
Grey	75	172	72	319
Light brown	63	242	51	356
Dark brown	14	264	288	566
	——	——	——	——
	499	960	541	2,000

VI. Diagnosis.

Diagnosis is made by noting the presence of a rotatory movement of the eyeballs. In most cases the diagnosis is easy, and there is no doubt about the presence of the disease. The following routine method should be employed. The patient should be asked to fix a pencil held about 12 in. in front of and on a level with his eyes. If movement of the eyes does not appear, gradually elevate the pencil, asking the patient to follow it with his eyes only, the head being kept level. Note the degree above the horizontal at which movement begins; this gives a rough test of the severity of the disease. If this fails, ask the patient to stoop quickly, and examine the eyes as soon as he returns to the horizontal position. The test may be varied by holding a mirror underneath the patient's head and observing the eyes while the man remains stooping. Before a negative opinion is given the tests should be repeated after the man has been kept in a dark room for half an hour, and an ophthalmoscopic examination should always be made. The rotation test advised by Reid, in which the man is spun round and round, should not be used, as nystagmus is produced in normal people in this manner. If, when asked to look up, the patient persists in raising his head and not his eyes, nystagmus is probably present. In these cases the test should be varied in this manner—one hand should be placed on the man's head to keep it flexed, the pencil should be held in the other hand, and the test continued as before. This method brings out the

Fig. 22.—The Head Test.

This is one of the best methods of bringing out the movements of the eyes and the tremor of the head so often present in nystagmus. The patient's head is kept strongly flexed with one hand and his attention is directed to the other hand held above his head.

Fig. 23.—The Head Test.

This patient (spastic type of disease) was asked to keep his head down and look up. Note the extreme convergence of the eyes—an involuntary protective mechanism for fixing the eyes and preventing oscillation—and compare with Fig. 22.

movements and any head tremor that may be present. At the same time a sense of great resistance on the patient's part to the continued flexion of the head will be felt. This sign is often given by patients in whom the movement of the eyes has disappeared, and is very similar to the tremor found in neurasthenia and in old age, but is generally of a coarser nature, and increases in intensity for some time. Nystagmus may be obtained easily one day and with difficulty the next, and for this reason a second examination is sometimes necessary.

When movement of the eyes is present its character must be noted. The true movement of miners' nystagmus is a rotatory one, and if the movement is purely lateral and unequal on both sides grave suspicions should be aroused. The case may belong to one of the group of nervous diseases, such as syringomyelia or disseminated sclerosis, which give the symptom of nystagmus. In these diseases the movement is generally lateral, and may be more marked on one side than the other. Even when the oscillation of the eyes in miners' nystagmus appears to be lateral there is never the quick jerk and slow return typical of disseminated sclerosis. A general examination should always be made if there is any doubt of the case. The list of diseases in which nystagmus is found is a very long one. Nystagmus may be congenital or acquired. In the congenital form it occurs in some rare diseases of the choroid or retina, such as retinitis pigmentosa, congenital cataract, and corneal nebulae. Nystagmus is always found in the complete albino. It is also sometimes found in cases of error of refraction. In the acquired form it is found first in the disease in question, miners' nystagmus; then as a symptom of one of the group of nervous diseases mentioned above; in toxic conditions; and finally, as Barany has shown, it may be present after rotation, syringing the ears with hot or cold water, alteration of air-pressure, or galvanism to the head (Brain, 29, p. 283). A more detailed list is given by Wildbrand and Saenger, *Neurologie des Auges.*

Voluntary nystagmus has been described by Nettleship. In one case there was a rapid lateral movement at will, in the second case a house surgeon was able to produce lateral nystagmus by strongly converging his eyes. Mauersberg describes two cases and quotes references to nine others. Stirling quotes one case of voluntary nystagmus.

Cases of high myopia give rise to great trouble in diagnosis; the movement present is not the typical rotatory one, but rather an unsteadiness of the eyeballs. If any such unsteadiness is present in an underground worker, a certificate is readily obtained, and it is almost impossible to contest such a case. It is in these cases that the 'secondary' signs, head tremor and lid-spasm, may be of value.

Lid-spasm. The presence of lid-spasm renders difficult and sometimes makes impossible the detection of ocular movements.

If repeated examinations, after prolonged stay in the dark room, do not disclose oscillation the diagnosis must rest on the history and credibility of the man, general appearance, gait, photophobia, head tremor, and head resistance, and the character of the lid-spasm

VIII. Treatment.

In the early stages of the disease change of work from the coal face to other parts of the pit, and the provision of an electric lamp, will often put off a threatened attack. If symptoms continue, the man should leave the pit and obtain work on the surface. Rest from pit work and surface employment are the only specifics for nystagmus, and medicinal treatment, except that directed towards the general health of the patient, is of little avail. Ohm has given various alcohols and sedatives with transient success.

Palliative measures for the relief of symptoms may be carried out. Headache and sleeplessness are relieved by application of the constant current to the temples. Photophobia in the present investigation has been relieved by the use of the latest form of Crookes's anti-glare glass, but the results have not been conclusive. It has been found as a general rule that the use of dark glasses delays recovery. Some patients experience great relief by resting in the green fields of the country. Correction of refractive error undoubtedly does relieve symptoms, and it should be made a rule to correct any error of refraction in a nystagmic patient.

It is always necessary to remember that in the incapacity and suffering caused by the disease the mental factor is of great importance. 'The eye has a greater influence on the mind than has any other part of the body' (Llewellyn, 22, p. 23). 'The eye is the most psychic of all our senses' (Stassen, 46).

The custom of many medical men is unfortunately to tell their patients that they must never go down the pit again unless they wish to become blind. This action is exactly the same as that of an ignorant nursemaid who frightens her charge with a bogey-man and perpetuates a 'fear' which might otherwise have been overcome. No man loses his sight from nystagmus. The first duty of a medical man is, as Stassen says, to assure his patient not only that the disease is not incurable, but that, on the contrary, cure is certain to re-establish the man's confidence in himself, and above all to take every care not to discourage him (46, p. 225).

To tell a collier that he should never go down a pit again is almost to pass a sentence of industrial death upon him.

It is not too much to say that surface employment plays as great a rôle in the treatment of the disease as work underground does in its production. Unfortunately it does not pay the colliery manager to give these workmen surface employment, for two reasons: (a) the high average former weekly wage which often necessitates the payment of £1 a week in half difference in addition to the usual surface wages, (b) the ca' canny policy which some workmen pursue. Every encouragement should be given to the men on full compensation to attempt surface work of any description wherever they can find it, and no reduction in compensation should be made, for say the first six months, for any wages the man receives in this way.

In the first instance the men should be allowed to work for one or two days a week, and this time should be gradually increased. It is not as a rule possible to give the men work for half a shift,

but if men are paid by the hour this would be a good method to employ in the early stages.

It has been suggested (64, 25) that after a certain period reductions should be made in the weekly compensation payments in order to stimulate the men to find work on their own account.

The returns given by the large indemnity societies show that a large proportion of men do return to underground work, and it is to be hoped, with the improved illumination which is being effected in our pits, that not only will the disease be gradually stamped out, but that men who have failed will be able to resume their old employment.

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PSYCHO-NEUROTIC SYMPTOMS ASSOCIATED WITH MINERS' NYSTAGMUS.

By W. H. R. Rivers, M.D., F.R.S.

Many observers of miners' nystagmus have noted the large extent to which the ocular troubles of this disease are accompanied by nervous or mental symptoms which cannot be regarded as the direct result of the affection of the eyes and eye-movements. Certain sensory or mental symptoms, such as giddiness, dread of strong illumination, and probably also headaches, especially when localized in the front of the head, can be ascribed to the disordered state of the eye-movements and accompanying disturbances of vision, but no such direct relation is to be discerned between the state of the eyes and such symptoms as general tremor, habitual rapidity of heart action, excessive sweating, abnormal anxiety, depression, forebodings, apprehensions, and disturbing dreams. These symptoms are of exactly the same kind as those which occur in other nervous and mental disorders. All were, for instance, prominent in the nervous and mental disorders which followed the strains and shocks of warfare. It is customary to speak of disorders of this kind collectively as psycho-neurosis, and for the sake of brevity I shall use this term.

It may now be accepted with confidence that the affection of eye-movements with its accompanying symptoms is primarily due to defective illumination. At the same time it is clear that the disabilities which oblige miners to give up work, and still more those which prevent their return to work, are not the direct result of the nystagmus, but are of a psycho-neurotic kind which have supervened, often after a long interval of time, upon the disturbance of eye-movements. It seemed desirable to the Miners' Nystagmus Committee to inquire into the psycho-neurotic aspect of the disease, and with this end in view Dr. H. W. Eddison was appointed to carry out the inquiry. Dr. Eddison worked for six months with the miners of Staffordshire, South Wales, and Yorkshire.

In his report to the Committee Dr. Eddison gives the following account of the mode of onset and development of the disease:

'The afflicted miner usually states that he could at first see fairly clearly the details of the part of the pit where he was working. As the years pass, however, he begins to feel that he is "straining" his eyes, and that the coal-face or other object of his attention appears to be nearer or farther away than it really is, and he experiences difficulty in focussing his eyes upon it. He can no longer see, for instance, the exact spot which he is trying to hit with his pick, nor can he fix his eyes definitely upon any particular mark on the coal-face, with the result that his eyes tend to move irregularly over a wider and wider area, with nothing very definite

to fix. Further, he may be obliged to guard against approaching within harmful range of other men's picks, or injury to himself or others with his own pick—another reason for taking his eyes off the already widened point of fixation. This stage may last for several months or years before the disease becomes "manifest". The usual subjective symptoms, described by Llewellyn, now make their appearance, and the man becomes apprehensive of his condition. His inability to fix objects in the pit makes him apprehensive of danger, which, in turn, renders him easily startled and lacking in self-confidence. He frequently has to stop work to rest his eyes, he screws up his eyes when he looks around him, and then finds that the lamps dazzle him, and appear to dance irregularly or to revolve rapidly in small circles. When he first observes this he screws up his eyes still farther, and so comes up to the surface. Here he finds that he is still farther dazzled by the daylight. This latter factor, aggravated by the anxiety as to the fate of his eyes, and incidentally of his income—all of which serve to keep the ocular condition at the focus of attention—perpetuates the blepharospasm with which are associated the blinking and over-action of the frontalis.'

Two symptoms which Dr. Eddison finds to be almost universally present are headache and giddiness. Over-excitability of the eyelids (blepharospasm) is frequent. Dr. Eddison finds that this symptom often occurs in cases where there is no nystagmus, and is inclined to regard it as associated with the psycho-neurotic rather than with the ocular aspect of the disease.

In those cases in which abnormal anxiety is present, a state usually known as anxiety-neurosis, Dr. Eddison distinguishes two groups. In one the prominent symptoms are disordered heart action, excessive sweating, and dilated pupils, with irritability and lack of concentration, while in the other group the symptoms are more purely mental and include irritability, depression, forebodings, apprehensions, and sleep disturbed by dreams accompanied by fear or other unpleasant emotions.

Tremors are common, the most frequent being a rotatory movement of the head. As this form of tremor is unusual in psychoneurosis generally, it can be definitely connected with the ocular aspect of the disease.

Taking the affection as a whole, Dr. Eddison distinguishes two main varieties : one beginning with nystagmus and the symptoms consequent upon it, upon which an anxiety state and abnormal fears supervene ; and a second group in which the psycho-neurotic symptoms are primary, or at least more prominent than those which can be directly ascribed to the state of the eyes. As already indicated, he includes in this group the cases in which affection of the eyelids is present. Many miners suffering from this second form of affection may be free from nystagmus, at any rate at times, and when the symptoms are accompanied by nystagmus Dr. Eddison believes that the two are not connected with one another.

Dr. Eddison gives in his report an account of a number of individual patients illustrating the extent to which additional factors, such as psychical conflicts of various kinds, sexual dis-

turbances, and domestic worries, have contributed to the production of the disorder.

The general result of Dr. Eddison's inquiry is that it shows clearly how large a part is often taken in the production of the general state known as miners' nystagmus by factors which have no direct connexion with the disorder of the eye-movements to which the term 'nystagmus' should properly be limited. His account makes it clear that in some cases the state known as miners' nystagmus may be a psycho-neurosis arising independently of any disorder of eye-movements or of vision, while in other cases the psycho-neurotic aspect of the disease, though secondary to nystagmus proper, has come to be the more important part of the disease.

An interesting problem, to the solution of which Dr. Eddison contributes several important facts, concerns the nature of the factors upon which the psycho-neurotic state depends. It is now widely held that psycho-neurosis is a means adopted by the organism unwittingly, whereby an attempt is made to solve a conflict between certain instinctive desires, on the one hand, and factors, chiefly of a social kind, on the other hand, which conflict with these desires. According to one school of thought, the instinctive desires which thus enter into the causation of psycho-neurosis are almost exclusively derived from the sexual instinct, and this mode of causation is probably largely true of most forms of such disorder as occur in ordinary civilian life, this instinct being that which, coming most frequently into conflict with social traditions and ideals, leads most frequently to repression.

To the other main school of thought the instinct of self-preservation, and especially the group of instincts which form the natural response to danger, take a prominent place in the production of psycho-neurosis and are almost exclusively responsible for the psycho-neuroses of war. Since the calling of the miner resembles that of the soldier in being a dangerous occupation, it seemed not improbable that it would turn out to provide another example of the production of psycho-neurosis through conflict between the danger instincts and social traditions and ideals. Dr. Eddison's report provides a certain amount of evidence in confirmation of this point of view.

In his account of the development of the disease Dr. Eddison notes how the loss of clear vision and power of definite fixation gradually leads to apprehension of danger and lack of confidence, and both of these factors would produce a state in which the miner works under continual strain, and thus provide favourable conditions for the occurrence of psycho-neurosis. Several miners acknowledged the existence of definite apprehensions of danger, especially after accidents to themselves or others had brought the fact of danger to their attention. In one case a miner who, according to the more usual rule, denied all thought of danger while working went on almost in the same breath to remark : 'those chaps who think about other things while they work in the pit soon get killed,' a remark pointing clearly to the repression of thoughts of danger.

Another indication of fear as an element in the production of

psycho-neurosis is the occurrence of this emotion in dreams, for it is an elementary feature of the psychology of the dream that repressed emotions find expression when the control exerted in the waking state is removed in sleep.

It is evident, however, that danger forms only one factor in the production of the psycho-neurotic symptoms associated with miners' nystagmus. There can be little doubt that the nystagmus itself plays a prominent part in the production of these symptoms. It has already been seen how the disturbances of vision accompanying nystagmus are themselves the causes of apprehension and serve to make manifest fears and anxieties which would in the healthy miner keep beneath the surface of his consciousness. A still more important way in which the nystagmus acts is that in most psycho-neuroses some special experience serves as a nucleus round which other symptoms tend to centre. Thus, in the psycho-neuroses of warfare some old wound or organic affection will determine the locality of an hysterical paralysis or anaesthesia; some especially disturbing experience, whether of warfare or of civil life, will occur in direct or distorted form as the central feature of a nightmare or of a terrifying image or thought of the day; or some abnormal tendency of childhood or youth will recur and form the central feature of the malady. Through the prevalence of nystagmus the miner is provided with such a nucleus for his psycho-neurotic symptoms, and it is therefore natural that affections more or less directly referable to the state of the eyes should bulk so largely among the symptoms of this form of psycho-neurosis. In the psycho-neurotic state the attention of the patient is apt to dwell on the unpleasant and the unfamiliar, and his disturbances of vision and related pains and discomforts connected with his nystagmus provide the miner only too readily with objects for his attention.

The mechanism of the production of psycho-neurosis secondary to miners' nystagmus makes it clear why compensation should have produced so great an increase in the number of those in whom nystagmus has produced a disability to work. Doubtless there are miners who have wittingly utilized their eye affection as the means of escaping from a disagreeable and toilsome occupation, even though they suffer a certain monetary loss, but far more frequently the relation between nystagmus and disability is of a more subtle kind. One effect of compensation has been to make nystagmus and its accompanying disturbances a subject familiar to every miner, and has therefore greatly enhanced its tendency to become a nucleus for his psycho-neurotic symptoms. Doubtless in the old days there were miners whose nystagmus produced some disturbance of vision, but, if they had occasional aches and pains, the two were not associated, either wittingly or unwittingly, and there was therefore no tendency to arouse the thoughts of illness and disability which take so prominent a place among the strains by which the genuine psycho-neurosis is produced. Now, through the fact and prevalence of compensation, nystagmus has become so familiar to the miner that it is at once seized upon as the cause of any aches, pains, or other disturbances of the normal course of his life, and provides a nucleus for psycho-neurotic troubles.

The question of immediate interest is how far Dr. Eddison's study of the psycho-neurotic aspect of miners' nystagmus will help us to deal with its prevention and treatment. If, as I have supposed, the nystagmus with its accompanying visual symptoms not only produces a sense of insecurity and consequent apprehension, but also itself serves as a nucleus for the psycho-neurotic symptoms proper, it is evident that the primary need is to get rid of the conditions to which the nystagmus is due. As already mentioned, there is now widespread agreement that the essential cause of the nystagmus is defect of illumination. In improving the illumination of miners we shall not only lessen the prevalence of nystagmus in the strict sense, but also of its psycho-neurotic accompaniments. Moreover, it is highly probable that the defect of illumination acts as a condition which enhances the psycho-neurotic aspect of nystagmus by increasing the element of danger, real or imaginary, so that in improving illumination we shall be attacking the troubles which are now disabling so many miners from two different sides. Since Dr. Eddison has shown (in this only confirming the work of earlier observers) that psycho-neurosis frequently occurs in miners independently of nystagmus, it is evident that by merely attacking the factors which produce nystagmus we shall not necessarily get rid of miners' psycho-neurosis. If, however, low illumination enhances the tendency to apprehension and consequent repression, the improvement of illumination should also lead to a diminution of those cases of psycho-neurosis in which nystagmus is absent.

The bearing of the psycho-neurotic aspect of miners' nystagmus upon the problems connected with compensation is more definite. We are here presented with a situation closely comparable with that presented by pensions in relation to the psycho-neuroses of war. There is no question whatever that the perfectly legitimate and praiseworthy measure by which those disabled as the result of the war should receive monetary compensation has through the highly complex nature of psycho-neurosis led to the actual production, and still more largely to the prolongation, of disability to work. Similarly, the great increase in the prevalence of disabilities from miners' nystagmus since the introduction of compensation shows that this measure, as legitimate and praiseworthy as the compensation of sufferers from the war, has through the complexity of the state produced a great increase in the prevalence of psycho-neurotic affections. It is quite certain that compensation has not increased the prevalence of nystagmus in the strict sense. It is solely through its action upon the psychical and psycho-neurotic aspects of the disorder that the increased frequency of disability has come about. Consequently it is only through studies of the psycho-neurotic aspects of miners' nystagmus, such as have been carried out by Dr. Eddison, that we can hope to understand the relations between compensation and nystagmus, and can hope to find a remedy for the very serious state of affairs which exists at present.

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TOXIC EFFECTS FOLLOWING THE EMPLOY-
MENT OF ARSENOBENZOL PREPARATIONS

CONTENTS

INTRODUCTION

The first report of the committee upon the manufacture, biological testing, and clinical administration of salvarsan and its substitutes (*Medical Research Council, Special Report Series*, No. 44, 1919) contained a short section (pp. 33–8) on ' Ill effects following administration of arsenobenzol preparations '. The present report contains an extensive survey of the literature concerning such ill effects with careful consideration of the foreign writings on the subject, many of. which, though appearing during the war, have only recently become available.

The committee have also had the advantage of considering evidence which has come before them on unpublished cases, and they have given particular attention to two important groups of cases occurring in military hospitals, one in England and one in Ireland.

The literature concerning active syphilis in the pre-salvarsan era has also been examined in order to assess as far as possible the value of the view, still held by many writers, that the fatalities and many of the ill effects observed occasionally after salvarsan treatment are due directly to the activity of the syphilitic virus, and not to the drug.

In addition to the detailed consideration of actual deaths described as following the administration of arsenobenzol preparations, reference is made to all types of ill effect which have attracted attention.

Some difficulties arise in connexion with the numerous substitutes for the original salvarsan compounds, which came into use during the war among the belligerent nations. Even in Germany certain modifications of Ehrlich's original salvarsan and neosalvarsan (e. g. ' Silber-salvarsan ', &c.) have been employed. It may be said at once, however, that no single arsenobenzol preparation, which has been extensively used, stands out from the others, including the original German preparations, as having been associated with an undue proportion of ill effects. Moreover, taking the fatal accidents alone, it is evident that such serious symptoms and morbid changes

as have occurred after the use of various arsenobenzol compounds manufactured in different countries have been of the same nature. It appears, in fact, that there are untoward consequences of the administration of arsenobenzol compounds which must be attributed to the general constitution of the drugs of this group, and not to any impurity or peculiarity in the composition of a particular brand or make. It appears, further, that these consequences of the treatment in general are of more serious significance than the occasional accidents due to faulty technique in administration, defects in manufacture or preservation of the drug, excessive dosage, or undue shortening of the intervals between doses.

Many more deaths following the use of salvarsan have been recorded in foreign literature, especially in Germany, than in this country. A study of the German literature of the subject before the war gives the impression of an eagerness in some quarters to disparage the new treatment, and suggests that personal feelings against the discoverer led to a diligent search for, and prompt publication of, any records which could weaken confidence in its efficacy and safety. Public opinion was eventually so seriously disturbed that the German Government was forced to take action, and two separate official inquiries were made, in 1914 and in 1917, concerning the value of salvarsan in treatment, and the injurious effects which were alleged to follow its use. The findings of these two inquiries are of great importance, and are considered in a special section of the present report. During the war, and since Ehrlich's death in 1915, German writings on the subject have been no less numerous, and the accounts of debates at medical societies, &c., show that the question still attracts the liveliest interest in that country. The medical literature of France, America, and other countries also contains numerous articles on the subject.

The medical journals of this country contain relatively few accounts of fatal and other ill effects following salvarsan treatment, and it may be that fewer have occurred. That deaths do occur in hospital practice is evident from occasional accounts of coroner's inquests in the public press. The problem of estimating the number of deaths after treatment with arsenobenzol compounds in private practice is obviously far from easy under present conditions, since any reference to this on the death certificate would necessarily suggest a diagnosis of syphilis.

A further point which may well hinder publication of such accidents is the anxiety lest it be inferred that the fatality was due to faulty administration of the drug. But it is perfectly clear, from a very wide survey of the existing literature, that very few of the accidents recorded can be ascribed, even remotely, to faulty administration. Many of the recorded fatalities have occurred in large and well-equipped venereal centres where thousands of injections have been made with the best results by the same highly trained men.

The committee hope that a plain statement of the rare fatalities and other untoward effects known to occur after the use of arsenobenzol preparations may encourage the communication to the Ministry of Health of details concerning such accidents, for it is

obviously only in the light of such information that investigation and measures with regard to their prevention can be successfully undertaken.

II. GENERAL REMARKS ON THE LITERATURE CONSULTED IN PREPARING THE REPORT

The thorough character of the investigations undertaken at large venereal or dermatological clinics into the ill effects attending treatment by arsenobenzol compounds renders the data thus obtained extremely valuable. Records of Army statistics, and of cases observed under naval or military control, also give much information of value, but unfortunately such accounts are relatively few. A large proportion of the extensive literature surveyed is made up of reports by individual writers on one, or at the most two or three cases, many of them very incompletely investigated. For final conclusions, such accounts are obviously of little value, and few of them need be mentioned in more than general terms.

The following remarks, which refer only to fatalities occurring after the administration of arsenobenzol compounds, may serve to exemplify the difficulties encountered in dealing with such unsatisfactory records.

For a critical review of the deaths said to follow the injection of arsenobenzol compounds it is clear that only those records of cases in which a complete necropsy was carried out are of any solid value. When this distinction is made, it is extraordinary how many, especially of the earlier recorded cases, must be discarded. In many no necropsy was made, while others showed various morbid conditions which, if previously recognized, would have definitely contraindicated the use of the drug. Incidentally, it is evident that, since the most rigorous physical examination may fail to disclose pre-existing disease, there is no way to prevent the rare occurrence of such accidents in the future.

A good example of the necessity for complete examination is furnished by a consideration of Obermiller's monograph (1913), in which fifty-six deaths are ascribed to salvarsan treatment. The weak points in this list have been seized on by many subsequent writers, such as von Zumbusch (1916), who rejects half of the cases as either incompletely examined or obviously due to some cause other than the drug. For instance, among Obermiller's fifty-six cases, one died of leptomeningitis, one was found at necropsy to have tuberculosis of the lungs and broncho-pneumonia, while in twenty-one cases no necropsy was carried out. This writer also, after dealing with Obermiller's figures, gives a list of twenty-two other reputed fatalities from salvarsan, collected from medical records between 1913 and 1916, with a full list of authors. In five cases of this series no necropsy was made, and in others some definite pre-existing organic disease was found. On these and other grounds von Zumbusch excludes, perhaps too rigorously, sixteen out of the twenty-two cases as not necessarily related to salvarsan administration.

III. THE VARIETIES OF ILL EFFECT FOLLOWING AD-MINISTRATION OF ARSENOBENZOL COMPOUNDS

There is no very satisfactory way of classifying the reputed ill effects of treatment with arsenobenzol compounds, but the following list includes the main conditions requiring consideration :

1. Immediate reactions, e. g. diarrhoea, vomiting, pyrexia, head-ache, and also the vasomotor or so-called 'anaphylactoid effects '—' crises nitritoïdes ' of French writers.
2. Effects involving the nervous system. The most important of these is the fatal so-called ' encephalitis haemorrhagica '.
3. Effects involving the liver. Clinically these may be grouped into :
   (a) ' Early jaundice ' coming on a few days after an injection. This is usually mild and evanescent, but may occasionally be more severe and persistent.
   (b) ' Late jaundice ', occurring not earlier than several weeks after *the end* of a course of treatment. This is usually more severe and prolonged than the early jaundice.
   (c) Acute yellow atrophy of the liver—often supervening on ' late jaundice '.
4. Exfoliative dermatitis, and slighter skin reactions. The former may be complicated by broncho-pneumonia or septicaemia and end fatally.
5. Various lesions reported much more rarely—acute haemorrhagic nephritis, ulcerative enteritis, aplastic anaemia.

In addition to these a number of complications may occur during salvarsan treatment which, although previously believed to result from the effects of the drug, are now generally regarded as relapses of the syphilis or as due to the toxins of the spironeme suddenly liberated by the action of the drug (Herxheimer reaction). These include affections of the nervous system such as deafness, cranial nerve palsies, and other forms of ' neuro-recurrence '.

IV. THE INCIDENCE OF ILL EFFECTS FOLLOWING AD-MINISTRATION OF ARSENOBENZOL COMPOUNDS

It is extremely difficult to arrive at a just conclusion as to the frequency of ill effects following administration of arsenobenzol compounds. The standards adopted in reporting on these vary enormously ; some observers include in their reports such slight ill effects as a small rise of temperature following injections, head-ache, and mild vomiting ; others consider these too trivial to mention. Even as regards skin affections, some include such minor forms as urticaria and mild herpes, others recognize only severe conditions, such as exfoliative dermatitis.

Even in the case of the more striking ill effects, such as dermatitis and acute yellow atrophy, there is the difficulty that these may be delayed for a considerable time after the last injection of the arseno-benzol compound ; and the connexion between the arsenobenzol

treatment and the complication may not be appreciated because the latter did not come under the notice of the medical man who carried out the anti-syphilitic treatment. Even when these delayed ill effects have come to the notice of the observer there has been in some reports a tendency to exclude them as independent of the arsenobenzol treatment ; for example, in the second German inquiry mentioned below, the reporters evidently considered that deaths from acute yellow atrophy of the liver and those following acute dermatitis were not connected with the arsenobenzol treatment.

Further, the tendency for some of the ill effects (e. g. jaundice) to occur in small outbreaks may lead to one series of cases treated with arsenobenzol compounds showing a considerably higher proportion of ill effects and particularly of fatalities than another.

For these and other reasons it is impossible to consider, as strictly comparable, statistics from such different sources as military hospitals and civil treatment centres in this country and from treatment centres in other countries. It is even difficult, except in the case of the more striking ill effects, to compare the statistics of one military hospital with those of another.

(a) British Military Hospitals.

The ill effects reported by three British military hospitals are embodied in the three tables below. In these, as in other military hospitals, it was considered desirable to give an intensive course of treatment, with the object of enabling men to return to duty as soon as possible. The records are for obvious reasons more complete than can be obtained under conditions of civilian life, as the patients were under military control ; the ratio of injections to cases is considerably higher than in civil centres. These considerations largely explain why the ratio of ill effects to cases was higher than that shown in civil centres.

Table I. *Military Hospital A.*

Out of 4,887 cases of syphilis treated with ' 606 ' or ' 914 ' between 1915 and March 1921, there were 126 cases with ill effects, more or less serious, as follows :

			Cases.	Percentage of cases of syphilis.	Died.
Malaise			16	0·33	
Urticaria		9		0·18	
Dermatitis (Mild 37, Mod. 13, Severe 17)		67		1·37	3
Herpes		20		0·41	
Total skin reactions		—	96		
Jaundice, or (Mild 6) Jaundice with Mod. Severe 3 Dermatitis (Severe 4)			13	0·26	
Cerebral			1	0·02	
Total			126	2·57	3

2·57 per cent. of the cases had some reaction.
The deaths were 1 in 1,629 cases, or 0·061 per cent.

<p align="center">TABLE II. Military Hospital B.</p>

In 18,500 cases of syphilis treated with 125,000 injections of ' 606 ' or ' 914 ', the following ill effects were recorded :

		Cases.	Deaths
Urticaria	Mild	69	..
	Mod. Severe	13	..
	Severe	7	1*
Erythema and Dermatitis	Mild	45	1
	Mod. Severe	23	..
	Severe	29	6
Arsenical Herpes—Mild		2	..
Urticaria and Jaundice		2	..
Dermatitis and Jaundice		5	1
		— 195	
Jaundice	Mild	24	1†
	Mod. Severe	21	..
	Severe	10	..
		— 55	
Total		250	10

* This patient was found dead in bed. Death was attributed to heart failure. As he had urticaria following intramuscular administration of '914' the death is included, although not due to urticaria.

† Died of ' empyema and V.D.H.'

Ill effects in 1·36 per cent. of the cases, or 0·2 per cent. of the injections ; 1 death in 1,850 cases, 0·054 per cent. ; or 1 death to 12,500 injections, 0·008 per cent.

<p align="center">TABLE III. Military Hospital C.</p>

In this hospital 26 deaths occurred in the period between 1916 and 1918 among 9,758 patients treated for syphilis with ' 606 ' or ' 914 '.

The following table gives a summary of the causes to which death was ascribed :

Cause.	Number of deaths.
Dermatitis and purpura	7
Encephalitis or acute cerebral symptoms	2
Jaundice and other liver affections	2
Nephritis	4
Acute arsenical poisoning	1
Gastroenteritis and congestion of the lungs	1
Lobar pneumonia	3
Pleuro-pneumonia	1
Tertiary syphilis (tentative diagnosis)	1
Addison's disease	1
Pulmonary tuberculosis	1
T.B. laryngitis	1
Hemiplegia	1
	26

Of these deaths only 7 were attributed at the time to arsenobenzol compounds, 5 being dermatitis and 1 acute arsenical poisoning. As, however, in the same hospital 19,779 cases of gonorrhoea had been treated with only 2 deaths, it is probable that a considerable number of the 19 deaths not attributed to arsenobenzol preparations had some connexion with the employment of these drugs.

If all the 26 deaths were considered as connected with the adminis-

tration of arsenobenzol compounds (which would not be a fair assumption), the ratio works out at 1 death to 375 cases. The true ratio of deaths attributable to arsenobenzol compounds is less unfavourable than this, but it is clear that this hospital experienced a much higher incidence of fatalities than the other two. The committee are satisfied that the records in Hospitals A and B were carefully kept, and therefore the explanation cannot be failure to report cases from these hospitals; the preparations employed were similar in the three hospitals, but information at the disposal of the committee indicates that the course of treatment was more intensive in Hospital C, and that the observation of patients under treatment was not so careful from the point of view of detecting signs of intolerance.

At the request of the committee an analysis was made of the record cards available from certain military hospitals in which syphilis had been treated. Unfortunately, cards with full information were not available for all the cases treated, and accordingly the analysis does not give complete figures. There was, however, no selection, so that the figures may possibly give a fairly good idea of the incidence of certain complications.

Table IV gives the combined figures for four military hospitals, two in France and two in England. The table is interesting because, so far as was practicable, the figures have been divided according to the particular preparation of ' 606 ' or ' 914 ' used. It is not certain that the first two columns refer always to German Salvarsan and Neosalvarsan. Where the cards merely stated ' 606 ' or ' 914 ' without the name of a particular preparation, or where the words ' Salvarsan ' or ' Neosalvarsan ' alone were used the figures were placed in these columns.

(b) Civil Treatment Centres in England and Wales.

Returns as to syphilis from civil treatment centres in England and Wales during the year 1920 are summarized in the following table :

Cases of Syphilis.

	Males.	Females.	Totals.
New cases in 1920.	28,799	14,006	42,805
Total cases under treatment	49,927	27,718	77,645

The 77,645 cases of syphilis received in all 298,011 injections of arsenobenzol compounds, i. e. less than 4 per case.

During the year 81 cases of ill effects were reported, including 14 deaths. Of the deaths, 3 were cases of congenital syphilis in marasmic children, in which it seems reasonable to believe that the injections had little or nothing whatever to do with the deaths. Another death in a patient with tertiary syphilis and a transverse lesion of the spinal cord was excluded as not causally associated with arsenobenzol treatment. Excluding these 4 cases there were 77 of ill effects, including 10 deaths.

The remarks above as to failure to report ill effects apply particularly to civil centres, so that these figures cannot be compared closely with those of the military hospitals. The ratio of deaths to

TABLE IV. Showing number and nature of complications after administration of various forms of ' 606 ' or ' 914 ' (four military hospitals).

	Salvarsan or ' 606 '	Neo-salvarsan or ' 914 '	Arseno-benzol (Billon) or Arseno-billon.	Novarseno-benzol (Billon) or Novarseno-billon.	Kharsivan.	Neo-kharsivan.	Galyl.	Luargol.	Two or more drugs.	Total
Total cases of syphilis summarized .	550	3,152	5,414	2,667	6,213	108	676	26	11,140	29,946
Total cases without complications .	517	3,104	5,295	2,637	6,106	108	673	25	11,001	29,466
Total cases with complications .	33	48	119	30	107	..	3	1	139	480
Jaundice .	7	14	38	7	58	..	..	..	63	187
Dermatitis .	12	19	51	11	33	..	1	1	54	182
Erythema .	..	7	3	..	3	..	1	..	2	16
Urticaria .	14	7	26	12	4	..	1	..	20	81
Cerebral symptoms, convulsions, &c. .	..	4	1	..	9	..	..	..	..	14

reported ill effects is higher in civil centres than in the military hospitals. It is noteworthy also that the ratio of injections to cases was considerably smaller in the civilian centres than in the military, and to some extent this may account for the lower incidence of toxic effects.

The following summary gives information about these ill effects in tabular form :

Ill effects associated with Treatment by Arsenobenzol Preparations.

Nature of ill effect.	Civil Centres in England in 1920.	
	Number of cases reported.	Number of deaths.
Jaundice ⎰ Mild	18	..
Moderate	4	..
Severe	6	3
No particulars (probably mild)	10	
	— 38	
Dermatitis ⎰ Mild	3	
Moderate	9	
Severe	8	3
	— 20	
Erythema	7	..
Pyrexia	3	..
Acute enteritis	1	..
Cerebral	2	2*
Vasomotor	3	1⟨
No particulars	3	1⟩
	—	—
	77	10

* One of these deaths said to be due to anaphylactoid or nitritoid crisis.
⟨ Death said to be due to Herxheimer reaction.
⟩ Doubtful if this death can be attributed to the drug.

If the doubtful cases and the doubtful deaths are included the figures show one death for every 7,764 cases under treatment during the year, and one death for every 29,801 injections. The ill effects reported amount to nearly one for every 1,000 cases under treatment, or 0·099 per cent. In relation to the number of injections the figures show reports of one case of ill effect in every 3,870 injections.

(c) SUMMARY OF AN OFFICIAL GERMAN GOVERNMENT MEMORANDUM (DENKSCHRIFT) RELATING TO THE SALVARSAN TREATMENT OF SYPHILIS AND THE ILL EFFECTS OBSERVED AFTER ITS USE.

In August 1918 there was issued, by the German Minister of the Interior, an official publication of eighty pages dealing with the above subjects. This memorandum has been accessible to the committee, and it is felt that a summary of its main contents will be of value when read in conjunction with the present report. In this summary it will be convenient to use the name ' Salvarsan ' as a generic term for the different preparations (salvarsan, neosalvarsan, silver salvarsan, &c.), in this case all being of the original German manufacture.

The memorandum consists of an introduction and two reports, showing the results of inquiries made in 1914 and again in 1917. The introduction states the reasons for the investigations. The

first report was made at the instance of the Imperial Chancellor, the Prussian Minister of the Interior and the Prussian Minister of Education, and deals with Prussian statistics on salvarsan up to 1914. The second report was made by order of the Minister of the Interior in August 1917, and dealt with figures from the whole of Germany. An appendix is attached giving the more important literature on the subject from 1910 to 1918.

Briefly stated, the inquiry of 1914 was the outcome of a campaign against Ehrlich's new arsenical preparations, conducted partly in medical journals by doctors opposed to the treatment, and also largely in the lay press. The further employment of salvarsan was condemned for various reasons, and the controversy shows evidence of much personal animosity. It was alleged that frequent ill effects followed the use of the drug, and these dangers were emphasized in a monograph by Mentberger, published from the Dermatological Clinic of the University of Strassburg in 1913. In this book it was claimed that up to that date there had been 274 fatalities following salvarsan, 115 of these occurring within three weeks after the injection of the drug. The retail price of the new preparations was also severely criticized : one writer stated that the actual cost of the ingredients of one kilogram of salvarsan was 8 marks, excluding the costs of manufacture, which were calculated to amount possibly to a further 7 marks per kilogram. In comparison with this the retail charge of the Höchst manufacturing firm was, at that time, said to be at the rate of 16,000 marks per kilogram. It was claimed that this price was extortionate for a useless and dangerous treatment. Both of these accusations were met, the monograph of Mentberger being criticized especially by Benario (1914), a member of Ehrlich's Laboratory, while the manufacturers pointed out their difficulties in making salvarsan, the great expense of the apparatus, &c.[1]

Nevertheless the attacks in the lay press and elsewhere continued, until finally a petition was presented to the Chamber of Deputies demanding the prohibition of salvarsan from use. As a result of this continued adverse criticism, the Prussian inquiry of 1914 was begun.

Inquiry of 1914.

This inquiry was addressed to the directors of University Skin Clinics, large hospitals, and Special Clinics for Nervous Diseases. Many questions were asked, but only those with a direct bearing on the problem of ill effects will be noticed here. Particulars of accidents were demanded, with any views as to their causation, and the number of fatalities.

The inquiry was answered by 353 clinics, and the replies referred to 288,942 injections of salvarsan into 74,018 patients,[2] from the earliest use of the treatment up to the end of 1913. Of the total number of injections, the great majority were intravenous, but about 22,000 were either subcutaneous or intramuscular.

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[1] The various profits of the manufacturers, middlemen, and retail chemists were fixed by statute in Germany in 1918.

[2] It will be observed that the ratio of injections to cases was less than 4 to 1, in contrast with the high proportion of injections to cases in British military hospitals.

Table of ill effects. Inquiry of 1914.

Necrosis (presumably at the site of injection) . . .	455
Blindness	1
Complete deafness	2
Partial deafness	7
Brain affections	46
Neuro-recurrences	168
Fever, nausea, vomiting, and vasomotor effects	no exact figures given.
Delirium and convulsions (not fatal)	14
Nephritis haemorrhagica	1
Severe Nephritis	1
Jaundice	8
Abortion	1
Polyneuritis	6
Deaths : considered due to salvarsan	12
,, not certainly due to salvarsan	12

With regard to the list of ill effects and fatal accidents included in the table, the committee's study of the details of the cases given in the report brings out the following points of interest.

The frequency of necrosis is explained by the fact that, in this early period, so many injections were given by the subcutaneous or intramuscular methods. With regard to the cases of ' neuro-recurrence ', such as deafness and brain affections (other than encephalitis haemorrhagica), it has since been generally recognized that these are to be regarded as effects of syphilis, and not of the treatment. The infrequency of jaundice as a complication (eight cases only) calls for comment. In considering the details of the fatal accidents reported, the incompleteness of the records is a serious defect. Of the twelve cases in which death was considered to be due to salvarsan, half had either symptoms or post-mortem lesions pointing to the occurrence of encephalitis haemorrhagica. In one case included in this group, acute leptomeningitis was found at necropsy, while in another tuberculosis of the intrathoracic glands and of the liver was present. One case evidently proved fatal from severe exfoliative dermatitis. Of the twelve deaths in which the influence of salvarsan was considered uncertain, several might well, in the light of later experience, have been placed in the first group. One patient died with fever, convulsions, and aphasia ; another with convulsions, but at necropsy no changes were observed in the brain ; another was cyanosed, delirious, and finally comatose before death ; another suffered from septic sore throat, a rash, and high fever ; while yet another showed acute suppurative catarrh of both the respiratory and alimentary tracts.

A subsidiary list of thirty-two deaths is given, but these include the cases in which salvarsan was given as a last resort ; in diseases wrongly suspected to be syphilitic (malignant tumours of brain, spinal cord) ; and in other fatal maladies, such as pernicious anaemia and leukaemia, in which the new arsenical preparations were being tried.

Second Inquiry of 1917.

Doubts had been cast on the value of the first inquiry by the opponents of salvarsan who declared :

1. That the general practitioner had had no opportunity to give

his experience, which for the most part was unfavourable to salvarsan.

2. That the questions were answered in such a way as really to show statistics of mercurial and not those of arsenobenzol treatment.

The newspaper campaign against salvarsan continued unabated, and a petition against salvarsan had again been presented to the Lower House. Accordingly, to allay any public alarm, the Minister of the Interior ordered a new inquiry on a much broader basis throughout Germany, and referring to the whole period from 1910 to 1917. This inquiry was addressed to directors of hospitals and specialists in dermatology and sexual diseases. It was not sent to general practitioners, since it was pointed out that perfect salvarsan technique required apparatus only possessed by specialists, and, moreover, that the practitioner must have far less experience to record than the hospitals and special clinics.

Answers were received from 254 sources, relating to 265,158 patients, and to 1,268,946 injections of salvarsan. Again, in this inquiry many questions were asked relative to the estimated curative value of the drug, its contra-indications, &c., as well as ill effects said to follow its use.

Most of the known complications of salvarsan treatment were referred to, such as early vasomotor effects, icterus, dermatitis, albuminuria. In this report neuro-recurrences are definitely placed among the complications of syphilis.

Seventeen deaths are reported as certainly due to salvarsan ; 28 in which salvarsan could not be excluded, but in which this drug was not proved to be the cause ; and 25 in which the reporters considered that there was only a coincidence in point of time between the death and the salvarsan injection.

Of the 17 cases in the first group, 12 died of encephalitis haemor-rhagica and 4 of what was considered to be acute arsenical poisoning ; while the remaining case (heart failure after a journey) seems hardly worthy of a place in this group. Of the cases in the second group, in which salvarsan as the cause of death was held not to be proven, 5 cases had extensive dermatitis, while 3 died with acute yellow atrophy of the liver. In the fatalities included in the third group, no points of interest arise.

Comparison of the 1914 and 1917 Reports.

A comparison of the two reports brings out little of interest as regards the frequency of the less dangerous ill effects following the administration of salvarsan, since exact figures are not available in many instances. An examination, however, of the fatal accidents reported in the two inquiries brings out statistical results which are of some importance. It must be recognized at the outset that the German figures are in many ways fallacious, and cannot be compared, for example, with the British military and other statistics available to the present committee. In the second German inquiry, for instance, 70 deaths are dealt with as occurring after the adminis-tration of salvarsan, but only 25 of these are acknowledged as true salvarsan deaths and have been used in drawing up the table given

below. All the cases of acute yellow atrophy of the liver and acute dermatitis are excluded from the list, and considered as ' deaths not certainly due to salvarsan '. In the British statistics, dealt with by the committee, such fatalities are, in the present state of our knowledge, definitely recorded as salvarsan deaths. On the other hand it would be incorrect to include the whole of the 70 deaths as due to the action of the drug, some of the cases being undoubtedly due to known fatal diseases, quite apart from syphilis, in which the arsenobenzol compound was being used as a last resort.

With these preliminary reservations the figures tabulated in the two inquiries may be set out as they stand.

In the 1914 report from Prussia, dealing with the years 1910–13, 12 deaths acknowledged as due to salvarsan are recorded among 74,018 patients, while 3 others, referred to in the 1917 report, should have been included under the first inquiry. Thus it appears from the corrected figures that, between 1910 and 1913, 15 acknowledged salvarsan deaths occurred among the 74,018 patients, i. e. 1 death among 4,935 patients.

In the second report of 1917, 17 deaths are considered to be certainly due to salvarsan. Four of these are found to have been included in the previous report, while the 3 omitted from the 1914 report have been transferred to the first column of figures (1910–13) in the table below. Thus 10 new cases are left, or a total of 25 fatal accidents in all (15 + 10) for the whole period 1910–17. This figure divided into the total number of patients (265,158), gives a death-rate of 1 in 10,606 patients.

The corrected figures are contrasted in the following table :

Number.	1910–1913.	Whole period 1910–1917.	1914–1917.
1. Of cases treated	74,018	265,158	191,140
2. Of injections	288,942	1,268,946	980,004
3. Of deaths acknowledged as due to salvarsan	15	25	10
4. Fatal-accident rate	1 in 4,935	1 in 10,606	*1 in 19,114

* This does not indicate the real death-rate. It does not include deaths from dermatitis and acute yellow atrophy (see p. 15).

Table V gives a summary of the figures from different sources mentioned in this report.

V. DESCRIPTION OF ILL EFFECTS OTHER THAN THOSE CONNECTED WITH THE LIVER FOLLOWING AD-MINISTRATION OF ARSENOBENZOL PREPARATIONS

(a) IMMEDIATE ILL EFFECTS (VASOMOTOR REACTIONS, HEADACHES, VOMITING, &c.)

Various symptoms have been included under the phenomena described as ' nitritoid crisis ', ' anaphylactoid ', ' shock effect '. Those mentioned in the literature include the following : extremely low blood pressure, syncope, pulmonary oedema, dyspnoea, vomiting, rigors, high fever, pains in the limbs and muscles, cyanosis, sensation of choking, urticaria, oedema of the subcutaneous tissues, especially of the face, swelling of the tongue. This list by no means

TABLE V. *Ill effects after Arsenobenzol Administration.*

Sources.	Total cases of syphilis.	Number of injections.	Jaundice.	Dermatitis & other skin lesions.	Cerebral symptoms.	Other complications.	Total complications.	Total deaths.	Ratio of complications to total number of cases.	Ratio of complications to total number of injections.	Ratio of deaths to total number of cases.	Ratio of deaths to total number of injections.
German inquiry of 1914 .	74,018	288,942	8	..	60	574	642†	56*	..	..	1 in 1,322	1 in 5,140
German inquiry of 1917 .	265,158	1,268,946	..	..	..	..	..	70*	..	..	1 in 3,788	1 in 10,984
Leredde's table (France)‡												
1910	..	..	..	..	..	..	..	..	..	..	..	1 in 3,000
1911	..	..	..	..	..	..	..	..	..	..	..	1 in 8,700
1912	..	..	..	..	..	..	..	..	..	..	..	1 in 18,000
1913	..	..	..	..	..	..	..	..	..	..	..	1 in 54,000
British Mil. Hospitals :												
A	4,887	39,036	13	96	1	16	126	3	1 in 39	1 in 310	1 in 1,629	1 in 13,000
B	18,500	125,000	62	188	..	..	250	10	1 in 74	1 in 500	1 in 1,850	1 in 12,500
C	9,758	..	..	..	..	..	..	26*	..	..	1 in 375*	..
Four British military hospitals combined table .	29,946	..	187	279	14	..	480	..	1 in 62	..	..	..
Civil centres in England, in 1921 . .	77,645	298,011	38	27	2	10	77	10	1 in 1,000	1 in 3,870	1 in 7,765	1 in 29,800

* Some deaths should be deducted as having no connexion with the treatment.
† Some of these complications would now be considered as not connected with Arsenobenzol treatment.
‡ Leredde's figures concern administration of arsenobenzol compounds in France. Full details are not given in his paper.

B

includes all the ill effects of this group which have been described, but shows their protean character.

The mildest and most common symptom-complex, occurring immediately after or during an injection, is as follows : flushing, dilated pupils, slightly increased pulse rate, and some dimness of vision. If suffering from stomatitis the patient may also complain of pain in the teeth. In more severe cases these symptoms are intensified ; the lips and occasionally the tongue may become somewhat swollen ; there is a feeling of constriction in the throat and upper part of the chest, with dyspnoea ; and tingling in the extremities. If standing when the reaction comes on the patient may fall. Still more severe cases may show urticaria either limited to portions of the body or spreading over almost the entire trunk and limbs. Very rarely the patients may become partially unconscious, and remain so for some hours. These symptoms have been observed more frequently after some preparations than others. Normally they occur in isolated cases and often in patients who are similarly affected after each injection. When a number of patients injected on any one day are affected, the fault usually lies with the qualities of the drug as prepared for injection, or with the speed of the injection. Thus silver salvarsan almost always causes vasomotor symptoms if injected in concentrated solution and quickly.

At times the face becomes pale and the pulse feeble, but this is usually the prelude to an attack of vomiting ; exceptionally these symptoms of syncope occur in patients who have fasted but are ' nervous subjects ', and the fainting is analogous to that often seen during or after any slight surgical operation.

Another type of early reaction occurs a few hours after the injection, and is usually of the nature of rigor, fever, and headache. It is much commoner after the first than after subsequent injections. Occasionally, severe vomiting, which may be accompanied by diarrhoea, follows a few hours after an injection. When this ensues in a large proportion of cases injected on the same day, it can often be traced to a fault either in the technique of preparation of the drug, or to some defect in the particular batch of the arsenobenzol compound employed. Herpes labialis is frequently observed in such patients a day or two after the main reaction has passed off.

The symptoms so far mentioned are by far the commonest ill effects following the administration of arsenobenzol compounds, but, although some of them may be alarming enough at the time, they are usually mild, and rarely, if ever, fatal. They may occur after the administration of any of the arsenobenzol compounds, even with the best technique, but are most commonly provoked by improperly prepared solutions and faulty samples of the drug.

The following examples, collected from the literature, illustrate cases in which

1. A new and doubtful preparation of arsenobenzol was employed.

2. A fault was present in the sample used for injection.

Sargent (1918) recounts an experience with a new product placed on the market in America early in the war at a time when the stocks of the German preparations gave out. This new product which was labelled ' Salvarsan (Arsphenamin) ', was manufactured under the

direction of the Höchst Farbwerke, and by the process employed in Germany for the manufacture of salvarsan. All the cases of syphilis in which this new preparation was employed developed alarming symptoms—extreme collapse, rigors, &c.—but fortunately no fatality occurred. Sargent evidently was greatly frightened by the severity of the reactions, and condemns the use of this very toxic preparation.

Ross (1918) reports a case in which a ' neo ' preparation was given, 0·45 gm. being injected in 100 c.c. of distilled water. It was noted at the time that the powder was slow in dissolving, and that the resulting solution was mahogany-coloured. Following the intravenous injection, severe symptoms set in at once—choking sensation, pains in the feet and hands, agonizing pain in the abdomen, followed by unconsciousness. Later, fever, vomiting, and rigors occurred, but finally full recovery took place. Some days later another neo-preparation was administered to the same patient without the slightest reaction.

Glaser and Langer (1921) give an account of an alarming group of vasomotor reactions, showing a curious selective choice among a series of cases treated with the same batch of neosalvarsan. Three patients received the drug as a first dose, four as a second dose, and sixteen as a third dose (0·45 gm). The whole of the third group (sixteen patients) were seized with illness within one to two hours after the injection. The symptoms were chiefly rigor or chilliness, headache, vomiting, fever, and collapse. Some recovered quickly but others remained ill for several days. All the patients in the first two groups were unaffected.

Pathology of the immediate ill effects.

The frequency of these immediate reactions after the administration of salvarsan has stimulated a large amount of research into their cause. It has been pointed out (Kolle, Schlossberger and Leupold, 1920) that the symptoms show a close resemblance to those seen in anaphylactic shock, and the resemblance has led some writers to assume that a reaction of the anaphylactic type is concerned in their causation. The evidence in favour of such an assumption is, however, slender, although it is accepted in a paper by Moore and Keidel (1921[a]) from The Johns Hopkins Hospital.

Swift (1912), in a paper entitled ' Anaphylaxis to Salvarsan ', describes experiments in which, after a preparatory injection of salvarsan mixed with guinea-pig's serum, into a guinea-pig, symptoms similar to those seen in anaphylaxis were observed on re-injecting a similar mixture.

On the other hand there is abundant evidence that the immediate reaction may be produced by the first injection of salvarsan. Moreover, information is available from various sources of a connexion between the rapidity with which a sample of salvarsan is precipitated from its solution, and its liability to cause symptoms of this kind, when injected into the patient. Danysz (1916) states that all the products (mono- and di-sodium) of arsenobenzol give precipitates in the presence of chlorides, oxalates, carbonates, sulphates, and especially the alkaline phosphates. These precipitates, if formed

quickly in solution, may render the product extremely toxic to experimental animals. He quotes experiments with rabbits in which a solution of arsenobenzol, rendered opaque in less than ten minutes by adding 0·8 per cent. sodium chloride, was injected intravenously. Immediate convulsions followed, resulting either in death or recovery, according to the dose employed. He states that he has confirmed Fleig's original observation that in such animals, a precipitate is found in the pulmonary capillaries, and concludes that it can now be positively assumed that the immediate reactions following the administration of salvarsan are due to the formation of a precipitate within the circulation. Widal and his pupils (1920) are also fully agreed that the reactions after salvarsan are in no way anaphylactic, but are due to flocculation or precipitation in the body fluids. All this evidence seems to bring the phenomena rather into relation with the large body of experimental work on the effects of injecting into the circulation various colloidal solutions, which have the property of forming precipitates with the blood and initiating changes similar to those which precede clotting.

It seems, therefore, right to advise the avoidance of all such terms as ' anaphylactic ' and ' anaphylactoid '. The acute vasomotor phenomena seen occasionally after the administration of arsenobenzol compounds should be described as such, without any reference to a doubtful explanation.

A certain degree of protection against the results of the intravascular precipitation described above is obtained in animals by the previous injection of atropine or of adrenalin, or by a preliminary injection of the precipitate-forming solution. The use of adrenalin in man was first advocated by Milian in 1913, who claimed that by its use he had successfully prevented the occurrence of vasomotor symptoms in a patient who had always previously exhibited them with severity.

The evidence on the whole seems to indicate that the production of these reactions is caused more frequently by inadequately alkalinated solutions of old salvarsan or by imperfectly soluble samples of neosalvarsan. The physical properties of the solution seem to be more concerned than the presence of any soluble and abnormally toxic impurity.

According to Reid Hunt, some preparations of old salvarsan which produce this effect when made up in the ordinary way cease to do so when the preliminary solution, before alkalination, is made with water heated to 60° C.

(b) Death from so-called Encephalitis Haemorrhagica.

In the literature examined, death from this complication has been reported so frequently as to make this section of importance. Taking into consideration the records of so-called ' salvarsan deaths ' in all countries, it would seem that about half of the fatalities have been shown by post-mortem examination to be due to encephalitis. It is obvious, however, that this estimate may be erroneous, since these cases are of such a striking clinical character that any one seeing them for the first time would be likely to report them in print.

The symptoms, moreover, come on within two to five days after an injection and end fatally, in the majority of cases, within twenty-four to forty-eight hours of the onset. They are therefore more obviously ' salvarsan deaths ' than are some of the other complications which do not occur until some considerable time after the administration of the drug.

There seems to be a consensus of opinion (Kerl (1916), Meirowsky and Kretzmer, &c.) that the onset of encephalitis haemorrhagica is commonest in the secondary stage of syphilis, but it is to be remembered that the majority of cases when they come under medical treatment are in the secondary stage. There is general agreement (Kerl (1916), Obermiller (1913), Tomasczewski (1913), Mentberger (1913), &c.) that the particular variety of arsenobenzol compound used is without influence.

Some characteristic examples of this type of fatality, collected from the literature, may be summarized briefly.

Lissauer (1917) describes one case. Two injections of 0·3 gm. and 0·45 gm. neosalvarsan at ten days' interval. Two days after the second injection became acutely ill. Headache and shivering, followed by clonic convulsions, loss of reflexes, and palsy. On the following day was completely comatose, and died.

At necropsy no evidence of disease in chest or abdomen. In the head, extensive softening was found involving the left optic thalamus and internal capsule. The right corpus striatum and optic thalamus showed several round haemorrhagic areas, about the size of a hazel-nut. Microscopically the brain showed also abundant small perivascular haemorrhages. Thrombi were recognized in some capillaries, surrounded by small areas of necrotic brain tissue. The liver and kidney were normal. No spironemes could be found in the brain, liver, or kidneys, and no arsenic could be detected in the brain or liver.

Von Zumbusch (1916). Girl, 19 years old, with rash of secondary syphilis. Five months pregnant.

On 10th January given 0·45 gm. sodium-salvarsan.
,, 19th ,, ,, 0·6 ,, ,,
,, 27th ,, ,, 0·6 ,, ,,

On January 31st, four days after the last injection, the patient was well and out-of-doors. On the next day she had fever, headache, delirium, and aphonia. On February 2nd she was comatose, with absence of reflexes, a strong Babinski's sign, and a converging squint. No convulsions are noted. Death occurred the same evening. Multiple haemorrhages and softenings throughout the whole brain. Subserous ecchymoses in various parts of the body. No evidence of antecedent disease.

A case occurring in the British Naval Medical Service.

Male, aged 32 years, admitted to hospital with a typical primary sore. Received two injections of 0·6 gm. novarsenobillon at six days' interval. On the third day, after the second injection, he had what was described as a ' rigor ', and was unconscious for about a minute. On recovery he remained in a dazed condition. On the following day he had an epileptiform convulsion, with clonic spasms and became unconscious.

Epileptiform fits occurred at frequent intervals until death ensued on the evening of the third day. Brain oedematous (50 oz.). Great injection of cerebral capillaries, and minute haemorrhages present. Liver normal. Arsenic found in all the organs examined—including brain and liver.

These examples are taken at random, and illustrate the clinical picture and the post-mortem changes. The main features may be summarized from the accounts of many cases as under :

1. Such cases have been met with after the use of various arseno-benzol products.

2. A few cases have been described after a single injection ; the majority have occurred after the second injection ; some have been met with after later injections.

3. The onset of illness is sudden, and occurs as a rule from two to five days after the last injection.

4. The clinical picture varies, but the commonest history appears to be roughly as follows. Intense headache is the initial symptom, and may be accompanied by fever, shivering, and vomiting. On the following day the patient suddenly has an epileptiform convulsion, with clonic spasms, followed by unconsciousness. The deep reflexes are lost, a positive Babinski's sign, squint, and various other signs indicative of involvement of the central nervous system may occur. Retention of urine is common. Epileptiform convulsions recur at intervals, and coma continues until death. A fatal result frequently supervenes within forty-eight hours of the onset of symptoms.

Pathology of Encephalitis Haemorrhagica.

Two views have been held with regard to the aetiology of this very fatal complication :

1. That it is really acute cerebral syphilis, intensified as a result of the injection (Herxheimer reaction).

2. That it is a direct result of the salvarsan, possibly in persons unduly susceptible to the drug.

An examination of the literature of active syphilis in pre-salvarsan days does not lend support to the first theory. It is true, as Citron (1919) points out, that active cerebral syphilis involving the cranial nerves was not then unknown. But such cases were infrequent, and no trace of any fatality resembling at all closely the peculiar clinical picture of encephalitis can be found in the older records of syphilis. Add to this the fact that no spironemes can generally be found in the cerebral tissues, and a strong case against the condition being regarded as acute cerebral syphilis begins to be built up.

The probabilities of salvarsan being the direct cause appear very great, and are supported by the experiments of von Marschalkó and Veszprémi (1912) referred to below. Examination of the brain for arsenic in these cases has given such variable results as to afford little help in the solution of the problem. In some analyses no arsenic was found ; in others the drug was present in abundance.

With regard to the histological changes in the brain, the published descriptions are in many cases extremely poor and meagre. As a rule the only changes referred to are small perivascular haemorrhages, with here and there areas of haemorrhagic softening.

The best account of the microscopic pathology of the condition appears to be that of von Marschalkó and Veszprémi (1912), founded on the lesions observed in a single but very typical case. Macroscopically, haemorrhages were observed in different parts of the brain, sometimes punctiform and sometimes larger. The latter were considered to be due to aggregations of smaller haemorrhages. Most of the lesions were found in the pons Varolii ; they were less abundant in the corpus callosum, temporal lobes, and lenticular nuclei. There were no signs either of softening or of inflammatory change.

The microscopic changes observed may be summarized as follows :

1. Numerous small haemorrhages, consisting of red corpuscles and very scanty leucocytes. No signs of breaking down of brain cells, and no evidence of softening.

2. Important changes were observed, apart from haemorrhage, in relation to some of the cerebral vessels. One group of capillaries was found entirely filled with hyaline thrombi. Some larger vessels contained red corpuscles so aggregated together as to be no longer individually recognizable. Other vessels exhibited typical parietal thrombosis, not completely obliterating the lumen, but still allowing a partial blood flow through the centre. The thrombus consisted partly of blood platelets, partly of these combined with fibrin, and also contained leucocytes in greater or less numbers.

3. The lungs, spleen, kidneys, liver, and stomach were all examined histologically. No thrombi were found in any of these organs, although all were markedly hyperaemic.

Lissauer (1917) gives brief details, closely similar to the above. He refers to the presence of thrombi in the cerebral capillaries surrounded by small zones of necrotic brain tissue.

These multiple minute lesions of cerebral capillaries associated with hyaline thrombosis and with haemorrhage have been known for a considerable time in connexion with fatal cases of malaria, fat embolism of the brain, and carbon-monoxide poisoning. They came into renewed prominence during the war in connexion with cases of poisoning by phosgene gas, and in fatal war nephritis. In the cases of gas poisoning the small thrombi were found not only in the capillaries of the white matter of the brain, but also in the capillaries of the lungs and glomeruli of the kidneys. They are to be taken as evidence of damage to capillary endothelium.

Von Marschalkó and Veszprémi, following the occurrence of the case reported above, undertook some experiments on rabbits which have a direct bearing on the nature of the lesion, and strongly suggest the responsibility of salvarsan for their production, either directly or indirectly. The animals employed were injected intravenously with salvarsan, a 1 per cent. solution being used for convenience. The main results were as follows :

1. All animals receiving a dose of more than 0·19 gm. per kilo died almost immediately.

2. Animals receiving 0·15 gm. per kilo died in a few hours.

3. Animals receiving 0·11 to 0·12 gm. per kilo died in two to two-and-a-half days.

In the third group symptoms identical with those of encephalitis haemorrhagica occurring in man were seen, and the animals died after repeated convulsions. Moreover, the brain showed similar histological changes, consisting of punctiform haemorrhages and hyaline thrombosis of capillaries, without any inflammatory change. The writers then went on to see if plain water containing a sediment or the bodies of dead micro-organisms could cause the changes. Their results showed that without the salvarsan such effects were never produced.

Although hyaline thrombosis of capillaries in organs other than the brain has not been observed in cases treated with salvarsan, there

is evidence pointing to damage of capillary endothelium elsewhere in the body. Jersild (1918–19), for example, in a fatal case of encephalitis haemorrhagica, reports the presence of multiple small haemorrhages in the liver, spleen, kidneys, and lungs, in addition to the characteristic extravasations in the brain. These small haemorrhages in other organs are also referred to in other published records of cases.

Stühmer (1919) describes three cases of great interest in relation to their bearing on the pathology of encephalitis haemorrhagica.

Case 1.

Two doses of neosalvarsan were administered to a young man at six days' interval. Two days after the second injection he developed headache, followed by epileptiform convulsions, coma, and death on the third day.

P.-M. Hyperaemia and oedema of the brain. Acute internal hydrocephalus. No haemorrhages or softenings. All other organs normal.

Case 2.

Treated with two doses of neosalvarsan at ten days' interval. On the day following the second injection, the whole body became oedematous, there was high fever, but no headache or convulsions. On the fourth day the oedema began to pass off, and numerous small haemorrhages then became evident under the skin.

Case 3.

Illness began on the day following the second injection, with the usual symptoms of headache, convulsions, &c. Trephining was immediately carried out. On opening the skull, the superficial veins were found empty of blood, while the membranes were distended with clear fluid, giving the impression that one could see deeply into the brain tissue. When the pia mater was punctured, a large amount of oedema fluid poured out. The blood vessels were then seen to fill up. Improvement followed the operation, but death finally resulted.

P.-M. Internal hydrocephalus ; oedema of brain, but no haemorrhages or softenings.

The writer discusses the relation between oedema and haemorrhage, and considers that oedema always occurs first, and in severe cases is then followed by haemorrhage. Similar examples of oedema of the brain, without haemorrhages, but with the typical symptoms of encephalitis, have been reported by others (Obermiller (1913) 2 cases, along with 21 others showing the typical cerebral lesions).

(c) Cases with symptoms suggesting Encephalitis Haemorrhagica, but ending in recovery.

Klewitz (1918) records one case in which all the typical symptoms— headache, convulsions, coma, unequal pupils, incontinence of urine, followed soon after the sixth injection of old salvarsan. The fluid obtained by lumbar puncture was clear and under high pressure (150–160 mm. of water), and three days later was still under considerable pressure (120 mm. of water). This specimen contained many red blood corpuscles, but on standing remained the colour of ' meat broth ', which was regarded as evidence of haemorrhage of some duration, not, however, due to the previous lumbar puncture. The patient made a complete recovery.

L. W. Harrison (1916–17) has met with two somewhat similar cases. (i) A young soldier developed a series of epileptiform convulsions fifty hours after the third injection of kharsivan and became

semi-comatose. Lumbar puncture was performed, and 20 c.c. of cerebro-spinal fluid removed. Ten ounces of blood were also withdrawn by venesection, and 20 minims of adrenalin chloride solution (1 in 1,000) injected subcutaneously. Half an hour later the patient was fully conscious, and complete recovery followed. Further injections of arsenobenzol compounds were given later without illeffect.

(ii) In the second patient a series of epileptiform convulsions occurred in a London street, a week after the last injection of salvarsan. On admission to hospital, he was stuporose, but not completely comatose. He was still in the same condition a week later when 15 c.c. of cerebro-spinal fluid were removed by lumbar puncture. Recovery was immediate and complete.

Treatment of Encephalitis Haemorrhagica.

In the first Memorandum of the Salvarsan Committee (p. 42) the following treatment was suggested for these cases. ' Bleeding to 18 or 20 ounces, lumbar puncture with the withdrawal of 15 c.c. of cerebro-spinal fluid, and the injection intramuscularly of $1\frac{1}{2}$ c.c. of 1/1000 adrenalin, all of these to be carried out as soon as possible after the onset of the symptoms, before the vital centres have become hopelessly involved.'

There is little to add, as a result of further study of the literature, to the above recommendations, except to take note of Ehrlich's (1911) advice to trephine the skull in such cases. There is, however, no indication in the literature that trephining has been carried out in more than a few instances, and no recovery following the operation has been published. It seems, however, to be a reasonable enough suggestion, where lumbar puncture, venesection, and the administration of adrenalin have failed.

Various writers (Lissauer (1917), &c.) have put forward preventive treatments, based on theories of aetiology (anaphylaxis, &c.) which appear to have no foundation in fact.

(d) Rashes and Exfoliative Dermatitis.

Skin reactions have been reported after the use of practically every arsenobenzol compound, although on the whole the ' neo ' preparations seem to be less toxic. Their severity and importance vary enormously, but in Great Britain and America, where encephalitis haemorrhagica is rare, exfoliative dermatitis is perhaps the commonest fatal complication of treatment by arsenobenzol preparations. There are several types of skin reaction, and their different characters depend largely on the sensitiveness of the patient to the drug, the amount of arsenic introduced into the body, and the degree of reaction of the skin. They are all, however, manifestations of one and the same kind of reaction, each phase of which shows its special clinical characters. A patient may pass through the various stages very rapidly, so that an initial urticaria or a discrete erythema may in 24 or 48 hours become a confluent erythema, a day or two later be vesicular or bullous, and subsequently pass into a generalized, exfoliating, and weeping dermatitis. On the other hand all the

various phases of the eruption may be seen on different parts of the body at the same time.

Unfortunately it is impossible to foretell if a given patient is likely to be unduly sensitive to the arsenical drug, and the most careful watch should be kept for any form of skin reaction, however mild.

Incidence of skin reactions.

L. W. Harrison (1916–17), refers to 124 cases of dermatitis among 10,000 patients treated with roughly 80,000 doses of arsenobenzol. Twenty-six cases are described as severe, 24 as moderately severe, and 74 as mild or fleeting. Eight deaths were known to have occurred. Parnell and Fildes (1919) record 38 cases of dermatitis among 1,250 men who had received 6,588 doses of neosalvarsan compounds. Only one case appears to have been very severe, and no fatality ensued.

Moore and Keidel (1921 [a]) report the reactions of the dermatitis group seen at the Johns Hopkins Hospital, Baltimore, during the period 1914–20. Twenty-one cases were met with in patients to whom approximately 47,000 doses of arsenobenzol drugs had been given. Two non-syphilitic patients treated with arsenobenzol preparations also developed dermatitis. These authors remark that skin reactions are three times commoner in the white than in the negro race. Among their severe cases of exfoliative dermatitis, five patients died, giving a death-rate in this group of 27·7%.

Dr. W. Herbert Brown, formerly dermatologist to 39 General Hospital in France, has analysed for the Committee 187 cases in which skin reactions occurred in that hospital. Like Parnell and Fildes, he found that the largest number of reactions occurred after the third injection, as is shown in the following table :

Skin reactions at 39 General Hospital (Brown).

Number of injection.	Number of cases showing skin reactions.
1st	5
2nd	23
3rd	67 (35·8 per cent.)
4th	21
5th	15
6th	11
7th	28
8th	17

Parnell and Fildes found that 48% of these reactions occurred after the third dose of the drug.

Clinical picture.

The following clinical account is chiefly founded on Dr. W. Herbert Brown's observations at 39 General Hospital.

The eruption generally occurs within 48 to 64 hours after an injection, but the interval may vary greatly. The first evidence of any toxic effect may be the outbreak of dermatitis, 6 to 8 weeks, or even longer, after the end of a course of treatment (7 to 10 injections). The true nature of these delayed skin eruptions (which present an interesting analogy with the so-called ' late ' jaundice)

is apt to be overlooked if the patient passes into other hands, and as itching is fairly common, fuel may be added to the fire by the action of a sulphur bath or ointment, ordered under the impression that the condition is scabies.

Site of the eruption.

There is no special site for the acute arsenical eruptions. They usually appear first on the trunk or limbs, and then may either become generalized rapidly or remain localized to certain parts. The earliest sites are commonly the outer aspects of the limbs and the dorsal surfaces of the hands and feet. The folds of the body, viz. elbows, groins, neck, and popliteal spaces, fairly often show the first sign of erythema. The occurrence of a rash during the administration of ' 606 ' or ' 914 ', no matter where or of what character, should arouse anxiety, and any further administration must be carried out with great caution.

Forms of eruption.

(i) *Erythema.* Much the most common form of skin reaction is an erythema which varies greatly in intensity, from a very mild redness to a deep red with a slightly purple tint. The milder eruptions are generally more localized to the trunk and flexures of the limbs. The erythema may be (1) scarlatiniform, (2) morbilliform, (3) erysipe-latoid—less commonly (4) a blotchy erythema without any definite character. The eruption pales under pressure, but very acute cases have sometimes shown a petechial or haemorrhagic element. The morbilliform type is the more frequent ; the individual spots may remain fairly discrete, or become confluent, as in acute confluent measles ; accompanying this there is usually some suffusion of the conjunctivae, with oedema of the eyelids. It may closely simulate a copaiba rash. In arsenical dermatitis the face is generally the last part to be attacked.

(ii) *Papular.* The degree of infiltration of the skin varies considerably, but in acute cases there is always a certain amount. Occasionally there is a small discrete papular rash, but a large and urticarial type is more frequent. The papular element rarely presents the true wheal-like character of urticaria : the individual lesions tend to be less sharply defined, are more papulo-erythematous and uniform in colour ; and lack the tense, sharply localized oedema of urticaria. When confined to the backs of the hands, forearms, and dorsal surfaces of the feet, the eruption might pass for *erythema multiforme.*

Liebkind (1921) describes a nodular eruption appearing on the face and extremities after the fourth injection of salvarsan, which persisted for $3\frac{1}{2}$ months and left some pigmentation. Hudelo and Rabut (1920) record cases of acute erythema with diffuse oedema of the dermis, giving the patient a bloated look, accompanied by grave general symptoms of toxaemia, oliguria, retention of chlorides, but no albuminuria.

Parnell and Fildes (1919) describe two cases with a follicular eruption localized to the buttocks and thighs. Itching is very variable, and may or may not be prominent.

(iii) *Exfoliative Dermatitis.* The cases that go on to a generalized exfoliation are usually accompanied by fever, malaise, headache, and faucial congestion. In the great majority of cases the general symptoms correspond very closely to the extent and severity of the skin manifestations, and in severe exfoliative dermatitis emaciation is a very prominent feature. The exfoliation is always preceded by an acute erythematous dermatitis of varying degree ; in the milder cases in which the dermatitis does not pass beyond the erythematous stage with slight infiltration of the skin, only the superficial layers are exfoliated in the form of very fine branny scales, whereas in the more severe cases the erythema, which originally may have been morbilliform or scarlatiniform, becomes confluent over large areas and much deeper in colour, sometimes with a cyanosed tint. The infiltration becomes more distinct, being most noticeable on hands, feet and ears ; vesicles or small bullae may form and rapidly rupture, and thus produce areas of acute weeping dermatitis, marked redness of the skin, exfoliation, crusting and scaling from the drying of the exudate. The whole body may be more or less uniformly affected, or the weeping and exfoliation may be confined to parts of the body, frequently the limbs. The ears, scalp, armpits, groins and the folds of skin are commonly affected. There is invariably oedema of the eyelids, with conjunctivitis and sometimes photophobia. The skin on the palms and the soles is usually shed in large thick pieces ; exfoliation takes longer in these parts than in others. Secondary infection frequently takes place, especially about the feet and hands, and the serous discharge becomes fetid. The very severe cases with universal implication of the cutaneous surface are very distressing : the patient's physiognomy completely changes, the emaciation becomes very striking, and there is great loss of hair of the scalp, eyebrows, and eyelashes, the whole body presenting the appearance of an acute scaling erythrodermia with serous crusts in places, or with raw weeping areas. The tongue becomes dry, red, and furred, the mucous membrane of the mouth and pharynx congested, and the patients complain bitterly of dryness of the mouth. The main complications are glandular enlargements with abscess formation in the groins and axillae ; bronchopneumonia or oedema of the lungs may supervene, and the case then usually ends fatally. When recovery occurs convalescence is protracted, the skin becomes very thin, atrophic, and usually assumes a red-brown pigmented tint.

Two very unusual cases have been described in which numerous sterile non-inflammatory swellings followed the subsidence of a typical exfoliative dermatitis ; these started three to five weeks after the onset of the dermatitis and strongly suggested pyaemic abscesses. The swellings appeared rapidly and varied in size from a bantam's egg to a duck's egg ; were fluctuating and very painful but did not tend to point ; on the legs they tracked down the subcutaneous tissue. They studded the legs, abdomen, trunk, and arms. Fraser (1919) describes the contents, in his case, as thick, gelatinous, slightly opalescent and stringy, free from pus and sterile. In an unpublished case Dr. W. H. Brown found the contents sterile, like thick pus, greenish in colour and not gelatinous.

When the hands and feet are involved the nutrition of the nails is almost always seriously affected, and they may be completely shed. On the other hand the nails may become greatly thickened and distorted. In some reported cases polyneuritis accompanied or

followed exfoliative dermatitis. Albuminuria is inconstant in exfoliative dermatitis ; it may or may not be present even in exten-sive cases.

(iv) *Pemphigoid Eruptions*. Nicolas, Massia, and Dupasquier (1921) report cases of arsenobenzol reaction with eruptions simulating very closely pemphigus foliaceus.

(1) In their first case the skin lesion began sixteen days after the fifth injection as small papules on the backs of the hands and feet, and then spread rapidly over the whole body, including the face, becoming vesicular and then bullous. The bullae remained discrete in places, but became confluent in others ; the whole picture simulating a generalized intense pemphigus—except that there was more inflammatory reaction and infiltration of the skin than in true pemphigus. When the bullae ruptured, the picture changed into that of an acute weeping exfoliating dermatitis, the scalp being the only part to escape. The buccal mucous membrane was not invaded. The reaction was most marked on the forearms, hands, legs and feet : on the palms and soles the whole epidermis was raised by one vast bulla which was filled with a fetid sero-purulent exudate. But in spite of the severity of the skin reaction, the nails were not affected ; there was no marked general reaction, and the urine remained normal. Recovery was complete within three weeks. (2) In the second case the manifestations began twelve days after five injections of novarsenobenzol (0·15, 0·3, 0·45, 0·6, 0·6 gm.), and its evolution closely resembled that in the previous case, though later gangrene of one foot—spreading from the toes to the ankle—supervened with loss of pulsa-tion in the popliteal artery. The general state was bad, and death occurred two months after the onset of the symptoms. There was no albuminuria at any time. (3) The third case started three days after the following weekly injections—novarsenobenzol 0·15, 0·3, 0·45 gm. First there was itching of the skin, rapidly followed by an erythmatous dermatitis more or less generalized, with oedema of face and legs, and then by bullae. General reaction was grave, with albumi-nuria, acute nephritis, and pulmonary oedema, but ultimately recovery was complete. It will be noted in these cases that the doses were comparatively small. The authors do not mention whether or not their patients were taking mercury at the same time.

(v) *Raynaud's syndrome with gangrene* is exceedingly rare, but Nicolas, Massia, and Dupasquier (1921) record a case after adminis-tration of novarsenobenzol, which is of special interest because the doses were small, viz. 0·15 gm., 0·15 gm. and 0·3 gm.

The patient, a healthy man aet. 28 with a doubtful history of syphilis and doubtful Wassermann reaction, had not had any previous symptoms of Raynaud's disease. The injections were given intravenously in the right arm, and three days after the first he had tingling in the fingers of the right hand with slight cyanosis, lasting only a day. A week later he received a second injection (0·15 gm.), and within a few moments the cyanosis and tingling reappeared in the right hand ; later the symptoms became more intense, and the ears were affected. This state of vaso-constriction, after lasting three weeks, passed off completely. After an interval of six weeks he came under treatment at another station and was given 0·3 gm., and immediately cyanosis and pain returned in the right hand and attacked successively the left hand, toes, nose, and ears. The symptoms became progressively worse until the terminal phalanges of most of the fingers became gangrenous. The ears, nose, and toes recovered. The urine was free from albumen and sugar throughout.

Pathology of the skin reactions.

It is now generally accepted that the rashes and dermatitis are the direct effects of the arsenical drugs employed, and are in no way dependent on the presence of syphilis. Cases of dermatitis have occurred, as has been already indicated (p. 26), in which arsenobenzol

compounds have been administered for other diseases, in the known absence of syphilis.

It may also be mentioned that Sicard and Roger (1918), while treating cases of general paralysis of the insane with massive doses of salvarsan as a last resort, found that skin reactions were eventually produced in all these patients. Examples of their experiences may be quoted.

Case 1. Pruritus, generalized erythema, and then icterus appeared and gradually improved ; but later intense exfoliative dermatitis supervened, with loss of the hair, changes in the nails, and pigmentation of the skin.

Case 2. After 8 gm. of salvarsan this patient suffered from albuminuria, icterus, and intense exfoliative dermatitis.

The same writers later tried the effects of smaller doses of arseno-benzol (0·15 to 0·3 gm.) over long periods on cases of general paralysis; towards the end of the second month, when the total dose was between 11 and 12 grammes, the following toxic symptoms appeared : pruritus, erythema and desquamation of the skin, trophic changes in the nails, loss of hair, and finally ulceration of the skin. They compare these changes with those described by Brouardel, as typical of chronic arsenical poisoning, and find that they are practically identical. It is fairly clear, therefore, that the rashes and dermatitis met with after salvarsan treatment, are manifestations of arsenical poisoning, appearing unduly early and even after small doses, in persons unusually susceptible to the drug.

Death following exfoliative dermatitis may arise in various ways ; bronchopneumonia is the most fatal complication, but death may also occur from general septicaemia due to cutaneous infection or from toxaemia. In rare instances ulcerative enteritis or aplastic anaemia may close the scene. Moore and Keidel (1921 [a]) summarize the results of necropsies on three fatal cases of exfoliative dermatitis as follows :

' In general, the necropsy findings were the same in the three cases studied. There were innumerable haemorrhages throughout all the organs, more intense in the lungs. gastro-intestinal tract, and kidneys. The haemorrhagic nephritis in one case was extreme. The bone-marrow, in two cases examined, was markedly aplastic, the outstanding feature being an almost complete absence of orderly leucopoietic centres. In two cases there were noted, especially in the lungs, areas of bacterial invasion without the usual cellular exudate. As previously pointed out, Winternitz and Hirschfelder found a similar non-cellular exudate in the pneumonia of experimental animals whose bone-marrow had been destroyed.'

Moore and Keidel and other American writers have drawn special attention to the peculiar changes in the bone-marrow and circulating leucocytes in exfoliative dermatitis, and have correlated these changes with the rare occurrence of fatal aplastic anaemia after salvarsan. The characteristic blood picture, which they found in fourteen out of sixteen cases studied, consists of a leucopenia with decrease in the neutrophil polymorphs, well-marked eosinophilia, and increase in the large mononuclear cells. The eosinophilia may be extreme, and one case has been reported (Hofmann (1919)) in which these cells numbered 60% of the leucocytes present, although figures over 25% are uncommon. It is evident that, in cases of exfoliative dermatitis, the bone-marrow shares in the damage, and that such patients are

therefore likely, on account of the leucocytic damage, to be especially susceptible to bacterial infection.

On the other hand it is possible that injury to the bone-marrow may, in some cases, depend upon the presence of bacteria in the circulating blood.

Purpura haemorrhagica may occur without any other skin manifestation, as in a case recorded by Hyman (1920) as a fatal case of jaundice. The patient, a female, had received a single dose of 0·4 gm. ' 606 '. About five days after the injection she began to suffer from increasing malaise, and a month later was slightly jaundiced. With increasing jaundice the patient progressively failed, and purpuric spots appeared all over the skin and visible mucous membranes, with coffee-ground vomit and blood in the stools. Necropsy showed numerous visceral haemorrhages; but the liver was free from the changes usually associated with acute yellow atrophy.

Prevention of the rashes and dermatitis.

The closest watch must be kept for evidence of commencing skin reaction. Itching may be troublesome before any rash is visible. The greatest care and judgement must then be exercised to determine whether the course of treatment may be carried on normally, or whether it must be interrupted or stopped altogether in favour of mercury alone.

(e) POLYNEURITIS.

This somewhat rare complication of arsenobenzol treatment has been described fully in an article by Beeson (1920), who refers to the chief publications on the subject.

In the majority of cases the condition has followed at an interval after the development of a dermatitis, but in other instances no complications affecting the skin have preceded it. According to Beeson, this variety of polyneuritis was first observed by Duhot in 1912, who gave an account of five cases in which large doses of ' 914 ' had been employed. These patients received 1·2 to 1·5 gm. of the drug every two or three days until four or five injections had been given. After an interval, the following symptoms and signs appeared —pain in the calves and soles of the feet, with subsequent development of oedema, erythema, and desquamation. In the more serious cases the plantar, Achilles, and patellar reflexes were lost, and paralysis finally ensued.

In other examples quoted by Beeson, where smaller and more usual injections of arsenobenzol have been given, the polyneuritis has most commonly been found to ensue four to seven weeks after arsenical treatment had been stopped on account of the onset of dermatitis.

Spillman (1914) has described the occurrence of severe polyneuritis after two injections of 0·4 and 0·3 gm. of arsenobenzol, given at ten days' interval. On the day following the second injection a profuse erythematous eruption was noted. One month later weakness in both legs supervened, associated with hyperaesthesia and paraesthesia. These signs were followed by paralysis with muscular atrophy of both limbs below the knee, the extensor muscles being

more affected than the flexor group. Full recovery followed after three months.

Beeson reports one of his own patients who developed dermatitis after a course of eight injections of neoarsphenamine. Wrist-drop and foot-drop occurred seven weeks after the dermatitis was first noticed, followed later by atrophy and complete palsy of all the muscles below the knees. Very slow recovery took place.

Sicard and Roger (1918), from their experience in giving very large quantities of salvarsan to cases of general paralysis, have drawn attention to a sign which may be of practical importance. They noted that bilateral obliteration of the Achilles reflex regularly occurred, while the knee jerks were rarely affected at the same stage. The loss of the Achilles reflex occurred at a time when signs of polyneuritis, such as pains in the limbs and muscular atrophy, had not appeared. They regard this sign as important, and as indicating extreme caution in further arsenical treatment.

An exactly similar polyneuritis, with or without dermatitis, has been described after acute arsenical poisoning (rat-poison), while in the well-known English outbreak (1901) of chronic poisoning due to the presence of arsenic in beer, similar peripheral neuritis, palsy and muscular atrophy, sometimes associated with exfoliative dermatitis, was also encountered.

(f) Ulcerative Enteritis.

This complication has rarely been reported, but, as indicated in the case described, may give rise to fatal results. The pathology of the lesion is not difficult to understand, the damage to the intestinal mucous membrane by the arsenic being evidently similar in nature to that met with in exfoliative dermatitis, in which haemorrhage into the intestinal wall is frequently found in fatal cases. It seems probable that slight degrees of damage to the gastro-intestinal mucosa may occur, and give rise to symptoms of short duration, without, however, going on to an intense and possibly fatal enteritis.

Krüger (1920) has reported the case of a young female, treated in the ordinary way with salvarsan and mercury. An intense necrosing enteritis supervened, finally leading to perforation of the intestine and fatal acute peritonitis.

(g) Damage to the Kidneys.

In cases of syphilis treated solely with arsenobenzol compounds damage to the kidneys is rarely met with, even after repeated injections. No records have been found suggesting the occurrence of a consequent glomerulo-nephritis, but evidence of damage to the renal epithelium has been seen in a number of instances. The degree of damage varies, and is indicated either by the temporary appearance of albuminuria and tube-casts, or in rarer instances by the onset of haematuria. Some of the latter cases have ended fatally from suppression of urine. It is noteworthy that, in death from encephalitis haemorrhagica, severe haemorrhage may be found involving the renal tissues, as well as in other situations.

It is very doubtful how far the terms ' acute nephritis ' or ' acute

haemorrhagic nephritis ' are really applicable in the strict sense to the acute renal damage which may follow the use of arsenobenzol, although they are commonly employed in the literature. The same objection applies equally to the use of the term encephalitis haemorrhagica, since all observers are agreed that signs of inflammation are conspicuously absent in the cerebral tissues affected.

A true syphilitic nephritis, using the term in its strict sense, is definitely known to occur, especially at the secondary stage of the disease, in cases which have remained untreated. The literature of syphilitic nephritis has been very completely reviewed by J. H. Stokes (1916), who describes its special characters. It is interesting to find that the treatment of syphilitic nephritis recommended as entirely successful by Stokes (1916), and by Elliott and Todd (1921), is the administration of arsenobenzol compounds. It is definitely stated, in both the articles referred to above, that experience has shown that mercury must be withheld as long as albuminuria persists, or the conditions are made worse.

So far then from being themselves common causes of nephritis, the arsenobenzol compounds have been used with good effect in the treatment of acute syphilitic nephritis. The acute renal damage occasionally seen, as a result of their administration, may quite probably be regarded as of the same order as that occurring in the brain in encephalitis haemorrhagica, and even in the hepatic complications associated with jaundice. Turnbull (1920) found severe parenchymatous degeneration of the kidneys in every one of six cases of death after salvarsan, associated with jaundice, and in two of these cases haemorrhages were also found in the renal tissues.

The frequent combination of mercury with arsenobenzol treatment adds another difficulty in a number of reported cases of ' nephritis ', and on critical inquiry it may be found that mercury had been given over a very considerable period of time. The effects of mercury on the kidneys under experimental conditions are well known, and before the introduction of salvarsan, nephritis had been described as a complication of the prolonged mercurial treatment of syphilis. It is difficult therefore in some cases to know whether to fix the responsibility for renal damage on the arsenobenzol, or the mercury, or both.

The Committee are aware of the severe necrotic changes in the renal epithelium which result in rabbits after injection of arseno-benzol compounds. Dr. Dale has informed the Committee that, in a large proportion of rabbits which have received a single very large dose of ' 606 ' (0·12 gm. per kilo) or ' 914 ' (0·2 gm. per kilo) for testing purposes, great necrosis of the renal epithelium, followed by calcification, has been found after death. Kolmer and Lucke (1921) have described in elaborate detail experiments in which single large doses of arsphenamine and neoarsphenamine corresponding to 10 to 14 times the maximal dose for human use were found to induce, in rats and rabbits, severe vascular damage in the liver, kidneys, supra-renals, and spleen. When 6 to 18 injections of disodium arsphena-mine were given to rats or rabbits in doses equivalent to 0·01 gm. per kilo, with intervals of only three days between the injections, they reported only inconspicuous tissue alterations that did not

appear to be sufficiently pronounced to interfere with the functions of the organs, similarly with multiple doses equivalent to 0·02 to 0·03 gm. per kilo of neoarsphenamine. These doses are somewhat in excess of ordinary doses for human beings and were given with shorter intervals between doses.

Tucker (1911) gives a brief account of two cases in which ' nephritis ' supervened after salvarsan treatment. One case ended fatally, apparently from suppression of urine, since after death no urine could be obtained from the bladder by catheter. In the second case copious albuminuria, with tube-casts, followed the treatment, but later the urine became perfectly normal again. No mercury had been employed in the treatment of these two cases.

Weiler (1911) gives records of three cases in which ' severe nephritis ' followed the administration of small doses of old salvarsan. No reference to mercurial treatment is made, and in every case the urine was normal prior to the injection of salvarsan. In the first case, a patient aged 25 years, suffering from a late secondary eruption, 0·45 gramme of old salvarsan was dissolved in 35 c.c. of distilled water, neutralized with deci-normal caustic soda, and injected into the gluteal region. Fourteen days later signs of nephritis are said to have supervened, with swelling of the legs. The patient did not seek medical advice until two months after the injection, when a diagnosis of acute haemorrhagic nephritis was made. At a later period definite albuminuric retinitis was recognized. In the second case, a patient aged 26 years, 0·4 gramme of old salvarsan was given intravenously in 200 c.c. of normal saline, after correct neutralization with caustic soda. Five days after the injection, albuminuria was found present, accompanied by epithelial and blood casts. Seven days later the urine was practically normal again. In the third case, a patient aged 32 years, 0·24 gramme of old salvarsan was given intravenously. Eighteen days later both albumen (0·5 per cent. Esbach) and casts were found in the urine. This writer also refers to a case published by Werther, of a seventeen-year-old girl who developed ' acute haemorrhagic nephritis ' after an intravenous injection of 0·25 gramme of old salvarsan. Complete recovery followed in about eight days.

The Committee have been informed of four unpublished cases in which acute haematuria, followed by suppression of urine, and ending fatally, has followed an injection of salvarsan.

Unpublished cases of severe albuminuria following arsenobenzol have been reported to the Committee by Dr. J. C. Buckley of Nottingham and Dr. Facey of Bournemouth. Dr. Buckley has furnished particulars of two cases, in one of which a fatal issue ensued. In both, prolonged mercurial treatment had been employed in addition to the administration of arsenobenzol, while in the fatal case mercury had been in use for fully six months prior to the employment of arsenobenzol. In the two cases reported by Dr. Facey mercury had also been used in addition to injections of arsenobenzol. One patient died, evidently from a true nephritis, since albuminuria, with tube-casts, was associated with oedema of the legs and feet. Death occurred more than four months after the onset of nephritis was recognized.

It is significant that, after considerable search, the Committee have been able to find so few records even of intercurrent nephritis arising during salvarsan treatment. At the same time the administration of arsenobenzol has been known to aggravate an existing nephritis, and it is generally held that the existence of nephritis is an indication for great caution in the use of the drug.

(h) Aplastic Anaemia.

This appears to be a very infrequent ill effect of the administration of arsenobenzol compounds. One fatal case has been reported by Gorke (1920), while Moore and Keidel (1921 [b]) refer to two fatalities of a similar kind. The latter authors suggest certain interesting relationships between the blood picture known to occur in acute exfoliative dermatitis following salvarsan, and in aplastic anaemia. The matter is referred to in greater detail in the section on dermatitis. (Vide p. 30.)

VI. DISORDERS OF THE LIVER FOLLOWING ADMINISTRATION OF ARSENOBENZOL PREPARATIONS

Among the ill effects which have been attributed to the use of salvarsan compounds, various disorders of the liver have attracted great attention. These disorders of hepatic function vary greatly in intensity, and the most serious of all—acute yellow atrophy of the liver—figures in continental literature along with encephalitis haemorrhagica as the most fatal complication of the salvarsan treatment of syphilis. The information, however, obtained by the Committee, from unpublished military records, suggests that dermatitis and its complications are actually responsible for a much larger number of deaths than is supposed, although for some reason such cases have not been so frequently recorded in foreign literature.

As is the case in many lesions of the liver, the occurrence of jaundice affords the most definite evidence of disease to the clinician, and the phenomena observed after the administration of salvarsan have been commonly described in relation to this obvious sign.

The subjoined summary of the literature follows the classification usually adopted, where three types of jaundice are distinguished.
1. 'Early' jaundice. (Benign jaundice. Ictère immédiat. Frühikterus.)
2. 'Late' jaundice. (Severe jaundice. Ictère tardif. Spätikterus.)
3. Acute yellow atrophy of the liver—generally as the sequel of late jaundice.

It must, however, be pointed out, that in the opinion of the Committee the classification is not wholly satisfactory, inasmuch as acute yellow atrophy of the liver may occur early, and benign jaundice late.

(a) Early (Benign) Jaundice.

In this condition the onset of jaundice occurs usually within a few days, sometimes even within a comparatively few hours, after an injection of an arsenobenzol preparation. It may occur after the

first injection, or suddenly appear after any one of a number of subsequent injections. This complication has been referred to by many writers, Klausner (1911), and Stümpke and Brückmann (1912) being among the earliest. Its occasional occurrence is known to all who have had a considerable experience of salvarsan treatment. It sometimes fades quickly without treatment in the course of a few days, but may be very persistent. There is little or no constitutional disturbance, and the derangement of hepatic function is apparently quickly readjusted. In a number of cases, the records of which have been examined by the Committee, further injections of arseno-benzol compounds did not produce any return of the jaundice.

The aetiology is not fully understood, and no opportunity has occurred of examining the liver histologically in cases which are certainly of this type. Methods of estimating, with any degree of certainty, the functional activity of the liver, are still at an early stage of development. Recent evidence suggests that, even in absence of symptoms, there may be interference with liver function after every course of arsenobenzol compounds (see p. 53).

Although, however, the occurrence of early and quickly fading jaundice can generally be regarded as a trivial complication of salvarsan treatment, it must be pointed out that rare cases are on record in which severe hepatic lesions were found after death, though jaundice was transient or entirely absent during life.

Stewart, Vining, and Bibby (1919) describe the changes found in the liver of a girl, aged 21, who had been treated for syphilis with four injections of galyl, the last dose being given three months previously. Death occurred one hour after a slight surgical operation, performed under ether. The liver was reduced in size (39 oz.), and in a condition of typical sub-acute yellow atrophy. On going into the clinical history, it was found that slight jaundice, of about two days' duration only, occurred ten weeks before death, and about a fortnight after the last injection of galyl. Otherwise there was nothing in the history to suggest the existence of any hepatic injury.

Nicaud (1920), in the course of a description of eight cases of early jaundice (ictères immédiats) and sixteen cases of late jaundice (ictères tardifs), refers to a patient who died soon after the third injection of salvarsan. There was no jaundice and no other signs of hepatic disorder, and death was due directly to a cerebral haemorrhage involving the medulla. Histological examination of the liver, however, showed extensive lesions, fatty degeneration, and atrophy of liver cells, with round-celled infiltration in the portal tracts. Nicaud, after concluding that the arsenic is the cause of the jaundice in cases of syphilis treated with salvarsan, insists on the importance of recognizing that the drug can bring about hepatic damage, which in some cases is undeniably severe, even in the absence of all clinical signs (jaundice, &c.) referable to the liver.

(b) LATE JAUNDICE.

By this term is understood a condition of much more serious disorder of the liver, with intense jaundice. It usually occurs several weeks, and often several months, after the termination of a course

or series of injections of salvarsan, but occasional cases are seen in which severe jaundice starts early.

The long period which usually elapses after the last injection of the drug, often after the patient has ceased to be under the observation of the medical man responsible for the treatment, renders adequate proof of the responsibility of salvarsan for the condition difficult. It is much less obviously an effect of the salvarsan than is encephalitis haemorrhagica, in which the onset of serious symptoms follows within two to five days after an injection. The same delay in the onset of jaundice is, however, frequently seen in trinitrotoluene poisoning, in which the responsibility of the drug is clear. This severe type of jaundice has been met with by practically every one who has been concerned with the treatment of syphilis on a large scale, and many descriptions of the main symptoms and effects are available.

The attention which has been paid to its aetiology seems thoroughly deserved, since it is certain that the development of fatal acute yellow atrophy of the liver is commonly a further complication of some of the cases described as ' late jaundice '. This point will be referred to in much greater detail below.

Late jaundice is a serious complication, both from the symptoms produced, and from its duration, but it is never fatal unless complicated by the development of acute yellow atrophy of the liver. The main features and course are most easily described by some brief references to actual observations.

Rehder and Beckman (1917) report twenty cases of ' Spätikterus ', none of which were fatal. The primary syphilitic infections had occurred from seven months up to fifteen years previously. Six cases were in the secondary stage of the disease, and five in the tertiary stage. Eight were cases of latent syphilis and one of ' parasyphilis '. The patients had received intensive treatment by old salvarsan, combined with mercurial injections. The onset of jaundice occurred from one to five months after the end of salvarsan treatment, and three days to four months after mercurial injections had ceased. In all cases the icterus was severe, and accompanied by enlargement of the liver, extending sometimes to 11 centimetres below the costal margin. Recovery was slow and gradual in all cases.

Fabry (1918) describes seven cases of 'late jaundice', all in cases of primary syphilis which had been given a very rigorous course of treatment. All had received ten doses of neosalvarsan intravenously, at five-day intervals, combined with intensive mercurial treatment lasting as a rule for eight weeks. The jaundice appeared suddenly in all cases, at a time when no symptoms or signs of syphilis were present. The Wassermann reaction was negative in every instance. The interval after the last injection of neosalvarsan was from eighteen days to two-and-a-half months in six cases, while in the seventh, the jaundice only appeared after eight months had elapsed.

Milian (1920) refers to two cases. The first was a woman of 50 years of age, suffering from tertiary syphilis. She was given six injections of novarsenobenzol (Billon) over a period of one month. Eleven weeks after the treatment ended, she was readmitted to

hospital with severe icterus. The second case was a young man in the primary stage, who had received seven injections of the same arsenical preparation. Several months after leaving hospital he returned with severe jaundice.

Pulvermacher (1917) records that, among 458 cases of syphilis treated with salvarsan, he observed one example of ' early jaundice ' and seven of ' late jaundice '. The latter occurred from six to twenty-one weeks after treatment had ended. He states that the amount of arsenic given varied considerably and that the degree and severity of the icterus did not bear any relation to the amount given. He points out that only one of the seven patients still had a positive Wassermann reaction, but was without any symptoms or physical signs of syphilis at the time.

Silbergleit and Föckler (1919) had the remarkable experience of seeing in one hospital, during a period of three months, eight cases of late jaundice terminating in recovery, and in addition thirteen other cases of the same type which went on to the stage of acute yellow atrophy. Their records are important from the comparison they were able to make between the patients with late jaundice who recovered, and those in whom acute yellow atrophy finally supervened. They state that, in the non-fatal cases of late jaundice, the onset of the illness was never so sudden or severe as in those in which acute atrophy occurred. In five of the eight patients who recovered, fever was never present at any stage. Nervous symptoms were also less severe, only one being mildly delirious, and maniacal excitement was never seen. In the eight cases of late jaundice, the liver was not enlarged at the outset, but in six of them very definite increase in size was made out during the illness, a return to normal size occurring gradually during convalescence. Enlargement of the spleen was never noticed. In four cases the stools were clay-coloured. Biliuria was present in every instance, and a trace of albumen in four of the cases. There were never signs of actual nephritis, and leucine and tyrosine were never found. The onset of jaundice in these cases was from 38 to 103 days after the last injection of salvarsan, with an average of 65 days, the actual figures being 38, 40, 47, 56, 65, 77, 96, and 103 days.

In five cases the syphilitic infection was recent (within a year), in two it was old (eleven and thirteen years), and in the remaining example the date of infection was unknown.

All the patients were soldiers between 26 and 40 years of age and some had already undergone courses of salvarsan and mercury without ill effects.

The course of treatment given to these patients must be classed as active, the average amount of the drug injected corresponding to about eight injections of 0·45 gm. of neosalvarsan, spread out over a period of two months. All cases received, in addition, mercurial injections during the course.

Strathy, Smith and Hannah (1920), working in a Canadian military hospital, reported a series of forty-seven cases showing symptoms referable to the liver, with eight deaths from acute yellow atrophy of the liver. The onset of the jaundice was seldom less than

five weeks after the last dose had been given. Various salvarsan substitutes were employed—neokharsivan, galyl, novarsenobillon, &c., but no single substitute could be blamed. It is stated that an intensive course of treatment was being given with a deliberate military purpose in view. This will be referred to later in discussing the eight cases of acute yellow atrophy (vide p. 42).

Todd's observations on jaundice in the Rhine forces will be found on p. 53.

(c) Acute Yellow Atrophy of the Liver following Arsenobenzol Treatment.

Many circumstances combine to attract attention to acute yellow atrophy of the liver. These are, especially, the striking clinical symptomatology, the extremely bad prognosis, and the mystery which has always surrounded the causation of the disease as met with under a wide variety of conditions, quite apart from syphilis and salvarsan.

It is impossible to deal adequately with the possible relationships of salvarsan as an aetiological factor, without taking into account many of the other aspects of the problem of causation.

Acute yellow atrophy, following arsenobenzol treatment, as has been already briefly indicated, generally appears to be superimposed on the condition of ' late jaundice '. With few exceptions (e. g. the Newcastle cases, reported by S. McDonald (1918) and some of the Cherryhinton cases referred to below) it occurs some weeks at least after the end of a course of treatment.

It may be stated at once that the main clinical features and the changes, found post-mortem, of acute yellow atrophy following salvarsan treatment differ in no important respects from those met with in other circumstances. The first and most obvious sign is jaundice, usually intense but often afebrile at first, and not thought to be dangerous. Then, quite suddenly as a rule, the clinical picture changes to one of acute hepatic insufficiency. Fever, vomiting, rigors, delirium, and other nervous symptoms appear, all of which are comprehended under the old clinical term of ' cholaemia '. Coma and death almost always result after a variable period.

Examination of the literature brings out certain curious points in connexion with the incidence of this complication. Although, as with other reputed fatal complications of arsenobenzol treatment, cases occur singly, several very remarkable groups of cases of acute yellow atrophy of the liver following salvarsan administration, have been met with in recent years.

Silbergleit and Föckler (1919) have published a very extraordinary series of cases, already mentioned in connexion with the description of ' late jaundice '. In a period of rather less than three months (from the end of December 1917 to the beginning of March 1918), in one hospital in Ingolstadt, they met with thirteen cases of acute yellow atrophy of the liver, all in syphilitic soldiers, and all occurring several weeks after the end of a course of salvarsan treatment. The patients were all treated by Föckler himself, who seems to have had a large experience of salvarsan work. During the

period mentioned, 650 other soldiers were treated by him without any ill effects. A fourteenth case of acute yellow atrophy of the liver also ensued about the same time but presented certain interesting and very peculiar features. It occurred in a medical officer aged $24\frac{1}{2}$ years, who was not known to have had syphilis, or injections of salvarsan, at any time. The Wassermann reaction, carried out shortly before death, was negative. The curious fact in connexion with the illness of this patient is that, while performing a necropsy on the first of the series of thirteen cases of acute yellow atrophy, he accidentally cut himself. No local reaction in the wound followed. Soon after this incident he was transferred to another hospital for duty, where three months later he fell ill, and died, the changes found post-mortem being typical of acute yellow atrophy of the liver. Unfortunately this death occurred at a distance from Silbergleit and Föckler, so that no particular questions were asked, and no examination was made of the veins at the bend of the elbows, &c., which might have thrown some light on the aetiology of this curious case.

During the same three months, eight cases of ' late jaundice ', ending in complete recovery, were also met with. These have already been referred to (p. 38).

The ages of the soldiers who died of acute yellow atrophy varied between 20 and 45 years, and, except for a case of tabes, none of them showed evidence of any pre-existing organic disease. This moreover was confirmed at necropsy.

This series of fatalities was so remarkable that a full account of the circumstances was evidently called for by a superior authority. This may partly account for the very complete details given in the paper, which is undoubtedly one of the most valuable accounts available for study.

The clinical features of the cases are well depicted. All fell ill suddenly while apparently in good health, rigor being the initial symptom in three cases. The chief early symptoms were giddiness, vomiting, and sometimes haematemesis. Fever occurred in most cases, but after two or three days the temperature fell to subnormal. In three cases there was no pyrexia at any stage. The appearance of jaundice practically coincided with the onset of symptoms ; in one instance a fleeting scarlatiniform rash was noticed on the skin. The pulse was as a rule slow at the outset, but not in all cases. Later, as the nature of the disease became manifest, severe nervous symptoms appeared in most cases, but the deep reflexes were never lost. In some instances the stools were clay-coloured, in others normal. Bacteriological examination of the stools for known pathogenic organisms was negative in every case. In the patients who died quickly the liver appeared diminished in size from the outset, whereas in the more prolonged cases the liver was at first enlarged, becoming smaller day by day. In every instance the liver was found to be smaller than normal at necropsy. In no case was the spleen enlarged during life. The urine always contained bile, and generally albumen in small amount. Leucine and tyrosine were never recognized in the urine as passed, but after more careful examination by a chemist these bodies were shown to be present

in four cases. With great fairness the writers point out two important facts in reference to this outbreak :

1. No animal experiments were carried out to exclude the possibility of spirochaetal (icterohaemorrhagic) jaundice (Weil's disease).
2. At the same period an epidemic of a rather peculiar type of paratyphoid B. fever was known to be present in the district.

While raising these questions, the writers bring forward good evidence against explanation on either of these lines ; thus it would be peculiar if only the syphilitic patients contracted either of these two diseases, since at this time there were over two hundred other patients with gonorrhoea and various skin diseases in the hospital, none of whom fell ill with jaundice ; moreover the mortality rate (13 deaths, 8 recoveries, i. e. the cases of ' late jaundice ') is far above the death-rate for spirochaetosis icterohaemorrhagica in Europe, and the clinical course of the illness was quite unlike that disease, in which the onset of jaundice is delayed for several days after the patient falls ill. They point out, also, as excluding the theory of paratyphoid B. infection, that examinations of faeces and urine in life, and of faeces, urine, and bile after death, were completely negative.

A similar and very remarkable outbreak of cases of acute yellow atrophy of the liver occurred in Cherryhinton Military Hospital, Cambridge, during 1917, resulting in the death of 15 patients. This outbreak is dealt with in full detail later in the report.

Stuart McDonald (1918) has published a preliminary report on an outbreak of five cases of acute yellow atrophy, all occurring in the same area within a period of two months during 1917. There is reason to believe that some but not all of these were military cases. All were syphilitic subjects, and in practically all cases a full course of intravenous injection of arsenobenzol compounds had been given, coupled with intramuscular injections of mercury. The syphilis was in no case of unusual severity. The series of cases is somewhat unusual in that their time of onset does not correspond to the period of ' late jaundice '. These five patients fell ill suddenly, two to eight days after the last injection of salvarsan. The main symptoms were icterus (at first suggesting nothing more than ordinary ' catarrhal ' jaundice), great mental excitement, haematemesis, and deep coma. Death occurred in one to four days after the onset of symptoms.

At necropsy, a great diminution in size of the livers was observed —the weight varied from 27 to 43 oz. There was usually intense necrosis rather than fatty degeneration of the liver parenchyma.

Cultures from heart-blood and lungs gave copious growths of organisms of the coli-typhoid group. McDonald suggests that in these cases there are at least two factors at work, and that the fatalities only occur when some special virus, e. g. a poison of microbic origin produced in the alimentary tract, acts on a liver already damaged.

G. Herxheimer (1920) gives an account of a series of six fatal cases of acute yellow atrophy, all in soldiers treated with salvarsan.

In all of these patients the icterus began as typical ' late jaundice ', from three to eight weeks after the course of treatment had ended.

Strathy, Smith, and Hannah (1920) met with eight fatal cases of acute yellow atrophy in a Canadian military hospital stationed in England during the war, among forty-seven patients showing symptoms referable to hepatic disorder — jaundice, decreased digestive power. Various salvarsan substitutes were employed, such as neokharsivan, galyl, and novarsenobillon, and in none of the fatal cases did the onset of symptoms occur sooner than five weeks after the course of treatment was over. The authors consider that an explanation of these cases is that an intensive treatment was employed, with the deliberate purpose of getting the men back to duty in an uninfective condition as soon as possible, and they state that the precautions necessary in such circumstances were in some instances relaxed ; for example, some patients received repeated doses after symptoms of arsenical poisoning had appeared (*Lancet*, 1920, i. 808). The course is said to have lasted seven or eight weeks, an injection both of salvarsan and of mercury being given once a week. The duration of the course corresponds closely with that given by Silbergleit and Föckler.

Henningsen (1916–17) describes one case of acute yellow atrophy in a woman of 25 years, with secondary syphilis, who was three months pregnant. She received three injections of salvarsan and thirty-nine mercurial inunctions. Nine days after the last injection, jaundice appeared, along with vomiting and diarrhoea. Death occurred after an interval which is not stated, and the necropsy showed typical acute yellow atrophy of the liver.

Scheel (1919) reports a closely similar case, in a woman also three months pregnant and suffering from secondary syphilis, who had received three intravenous injections of salvarsan, and frequent mercurial inunctions. At necropsy the liver weighed only 700 grammes, and showed the changes characteristic of acute yellow atrophy.

Lynch and Hoge (1919) report cases of especial interest in relation to the intensive form of anti-syphilitic treatment they have employed. They have been accustomed to give arsphenamine in doses of 0·4–0·6 gm. every week for six or eight weeks, followed by a month's rest, and then by a repetition of the course. They have had three cases of toxic jaundice, all severe, and one ending fatally from acute yellow atrophy of the liver. The writers themselves suggest that the intensive method of treatment adopted may have had something to do with the occurrence of these cases of liver disorder.

(*d*) Jaundice and Acute Yellow Atrophy of the Liver occurring during the course of Syphilis in pre-salvarsan Times.

Both jaundice and acute yellow atrophy of the liver have been described as effects of active syphilis long before the salvarsan era.

In British literature, a historical account of great interest is to be found in Wickham Legg's *Bile, Jaundice, and Bilious Diseases* (1880). His references to the occurrence of icterus in syphilis go

back to an observation of Paracelsus, quoted by Gruner (p. 134) in his book published at Jena in 1789 : ' Icterus cum morbo gallico copulatus non curatur nisi subacta materia venerea.'

It was early recognized (Ricord, 1851) that jaundice appeared most frequently at the beginning of the secondary stage. Gubler collected seven such cases, in all of which the icterus accompanied the syphilitic exanthem, and was preceded by digestive troubles such as nausea and pain in the epigastrium. None of these cases had received even mercurial treatment. All of them recovered, and the duration of the icterus varied up to a fortnight.

Lasch (1894) in an essay on ' Ikterus Syphiliticus Precox ' gives an account of forty-nine cases of jaundice occurring in the early stage of syphilis. His work was translated in the *Selected Essays and Monographs of the New Sydenham Society* in 1900. In addition to simple jaundice one case is described (footnote, p. 149, of the translation) of a female with obvious early signs of syphilis and jaundice of moderate degree. She was placed on a course of mercury, during which acute yellow atrophy of the liver developed, and proved fatal. Lasch definitely recognized, even at this early period, two types of jaundice in syphilis :

1. Simple icterus of short duration.
2. Severe icterus sometimes going on to acute yellow atrophy.

G. Herxheimer (1920), in the course of an article on acute yellow atrophy in syphilis, refers to the observations of Werner (1897), who met with fifty-seven cases of jaundice, in early syphilis, during a period of nineteen years in the Krankenhaus St. Georg, Hamburg. Herxheimer further states that the occurrence of icterus in the early stages of syphilis in the pre-salvarsan days varied between 0·37 and 3 per cent. in different published accounts.

With regard to the occurrence of acute yellow atrophy in syphilis in pre-salvarsan days, Wickham Legg gives some valuable information. Out of one hundred cases of acute yellow atrophy collected from the literature by this writer, eight were definitely known to be syphilitic.

Robinson (1865) gives the history of a drummer-boy, aged 20 years, known to be infected with syphilis, who died while jaundiced. The liver at necropsy weighed 2 lb. 8 oz., and was deep yellow in colour with numerous dark purple patches.

Andrew (1866) gives an account of a man aged 20 years, who died in St. Bartholomew's Hospital. He had contracted syphilis five months previously. On admission he was jaundiced, wildly delirious, and soon became comatose and died. A faint syphilitic rash was present on the trunk. The liver weighed 1 lb. 15 oz., was of orange red colour, and almost diffluent. There was great atrophy of liver cells, and leucine and tyrosine were found.

Richter (1898) published a collection of forty-one cases of acute yellow atrophy, all in florid syphilitics. It is curious that only five of these were males, while in the large number of females, only three were pregnant at the time of death.

Fournier (1906), in his well-known text-book on syphilis, gives a clear account of the disorders of the liver met with in the disease. He states that the liver is affected only rarely in secondary syphilis. Both benign jaundice and icterus gravis can, however, occur at this

stage, and the latter may end in fatal acute yellow atrophy. With regard to benign jaundice, he states that its mechanism is purely speculative, but it is inferred to be due to syphilis : (1) because of its chronological association with the secondary period, and (2) because no other cause is apparent. It generally coincides with the skin eruptions, about the third to the fifth month after infection. It ends favourably, after a duration of from two to four weeks. Fournier, at the time when he wrote, was aware of more than twenty-five cases of icterus gravis reported in the literature of secondary syphilis, and for a bibliography of these cases refers to a memoir by Gastou on *Ictère grave syphilitique secondaire*, about to be published in 1906. He points out that this type of jaundice generally supervenes on the top of the ordinary benign type and soon presents the usual features of acute yellow atrophy of the liver—delirium, dyspnoea, coma, and haemorrhages.

Parkes Weber (1909) describes a single case of acute yellow atrophy in a young man, infected with syphilis two months previously, and treated with mercurial inunctions only. This paper is important, because the writer gives a very full bibliography of the literature of acute yellow atrophy in syphilis from the earliest times up to 1908, detailing fifty-three cases of acute yellow atrophy from this cause.

Raw (1918) refers to his past hospital and asylum experiences. In the course of 6,000 necropsies he has seen 7 cases of acute yellow atrophy. In all there was a definite history of recent syphilis, and in only two instances had there been any recent mercurial treatment. All the cases occurred before salvarsan had been introduced.

(e) Acute Yellow Atrophy of the Liver in the Absence of Syphilis.

It is well known that, in the older literature of acute yellow atrophy of the liver, the aetiology in most of the cases remains obscure. The reader is referred to the text-books on hepatic diseases by Wickham Legg and Rolleston for the truth of this statement. Excluding the known syphilitic cases, the only factor in aetiology which has long been recognized to be of some importance is the frequent association of the pregnant state with the onset of acute yellow atrophy in females. Formerly, phosphorus poisoning was generally cited as a cause, but it is now recognized that the pathological changes in the liver in phosphorus poisoning differ in many respects from those of acute yellow atrophy. Since the diagnosis of syphilis has been rendered so much more exact in recent years, it may be well to quote some recent experiences of acute yellow atrophy of the liver in the known absence of syphilis.

Umber (1920) states that during the past eight years he has seen ten cases of acute yellow atrophy of the liver, seven within a year, and four within a few weeks of his article being written. Of these ten cases, nine were proved not to be syphilitic, and he believes the cause to be an acute ascending cholangitis. This view will be referred to later, but here it is enough to quote briefly one of his cases. The patient was a female, in whom icterus and high fever preceded

death. The Wassermann reaction was negative. A necropsy was performed very soon after death, and a typical acute yellow atrophy of the liver, associated with a haemorrhagic gastro-enteritis, was found.

Riess (1920), who states that his first publication on acute yellow atrophy of the liver was written in 1869, reviews the present position of the subject, and comments on its increased frequency at the present time. He states that his own personal experience of the disease consists of fourteen cases, not one of which was syphilitic. He therefore tends to discount both syphilis and salvarsan as causative factors, and suggests again the possibility of an acute ascending infection from the intestine.

(f) HAS ACUTE YELLOW ATROPHY OF THE LIVER BEEN MORE FREQUENT SINCE THE INTRODUCTION OF ARSENOBENZOL PREPARATIONS ?

This question can be approached in two ways : first, by a consideration of statistics relating to the incidence of acute yellow atrophy ; and secondly, by correlating experiences of individual observers favourably situated for a study of the problem. Obviously also two separate questions are involved : (1) Has there been any increase in acute yellow atrophy in recent years *quite apart from cases of syphilis treated with salvarsan ?* ; and (2) Has there been an increase of acute yellow atrophy in cases of syphilis treated by the newer arsenical drugs ?

With regard to the statistical question of increased frequency of acute yellow atrophy in general, the period of the war introduces certain difficulties. This is because, as is referred to in the next section, certain munitions of war, especially trinitrotoluene, were proved to be the occasional cause of acute liver atrophy. Most of these deaths in munition workers would presumably be placed in the Registrar-General's returns under the category of ' deaths from poisoning ', but it is possible that some of the delayed cases would be included as acute yellow atrophy among the statistics of hepatic diseases. With these provisoes, it is of interest to consider the Registrar-General's returns of icterus gravis and acute yellow atrophy of the liver, covering the period 1913–19.

These figures show that the numbers of deaths in females over 15 presented little difference in the period 1916–19 as compared with 1913–15, whereas in the case of males there was a large increase in the deaths at age-period 15–45, with a reduction for age-period 45 and over. It will be noted, from a comparison of the two periods 1913–15 and 1916–19, that there is no increase in the incidence of acute yellow atrophy, but rather a small decrease, in females between 15 and 45, and in males over 45 years. On the other hand, in the case of males between the ages of 15 and 45 there is a very great increase in the second period—from a yearly average of 6·66 in 1913–15 to 16·5 in 1916–19. It is known (see table) that more than half of the deaths in the period 1916–19 occurred in members of the fighting forces, and it is probable that there was in a number of these men an antecedent history of syphilis and treatment by arsenobenzol compounds. From these statistics the probable inference can be drawn

that in England and Wales there has been in recent years no increase
in the incidence of acute yellow atrophy of the liver, except in men
of a certain age group, more than half the cases in this group being
soldiers or sailors.

*Deaths from Acute Atrophy of the Liver in England and Wales in
Persons over 15. (From Returns furnished by the Registrar-
General.)*

| | Number of deaths, | | | | | | Total, | | |
| | 15–45. | | | 45 and over. | | | 15 and over. | | |
	Males.	Females.	Persons.	Males.	Females.	Persons.	Males.	Females.	Persons.
1913	7 (1)	20	27	7	7	14	14 (1)	27	41
1914	11	29	40	13	10	23	24	39	63
1915	2	18	20	11	8	19	13	26	39
1916	16 (6)	23	39	3	12	15	19 (6)	35	54
1917	17 (10)	16	33	9	13	22	26 (10)	29	55
1918	19 (15)	20	39	11 (1)	11	22	30 (16)	31	61
1919	14 (6)	25	39	6	5	11	20 (6)	30	50
Average per year									
For 3 years									
1913–15	6·66	22·33	29	10·33	8·33	18·66	17	30·66	47·66
For 4 years									
1916–19	16·5	21	37·5	7·25	10·25	17·5	23·75	31·25	55

Note.—Figures in brackets refer to men belonging to Naval or Military services. It is not
known whether these cases were syphilitic or had been treated with salvarsan.

Statistics of another kind have been made available to the Com-
mittee through the courtesy of Professor H. M. Turnbull, pathologist
to the London Hospital. His figures include a record of all the
necropsies carried out in that institution since 1907, and the cases
of liver atrophy met with during that period. These examples of
liver atrophy are to be the subject of a special report by Professor
Turnbull, but meantime the following table brings out certain
important points.

TABLE VI. *Professor H. M. Turnbull's figures from the London
Hospital.*

Year.	Total autopsies.	Males.	Females.	Cases of liver atrophy.
1907	1,150	666	484	2
1908	1,272	742	530	0
1909	1,271	732	539	1
1910	1,194	684	510	2
1911	1,252	737	515	1
1912	891	524	367	3
1913	868	503	365	1
1914	772	460	312	1
1915	706	463	243	1
1916	636	414	222	2
1917	565	349	216	1
1918	606	370	236	0
1919	595	362	233	0
1920	671	396	275	3
Totals	12,449	7,402	5,047	18*

* Adults, 11 (females 9, males 2); children below seven years, 7.

It will be observed that among the general civilian population treated in this large hospital there has been no increase of cases of acute liver atrophy during recent years. Of the eighteen cases met with in a period of fourteen years, only eleven occurred in adults, seven being in children below the age of seven years. In not a single instance was evidence of present or past syphilitic infection found at necropsy, or after histological examination of the organs. Of the eleven adults, nine were females. None of the females were pregnant.

Turning now to the experiences of individual observers, opinion on the subject is divided in certain respects. There is, however, a considerable accumulation of evidence in the literature that during the period of the war acute yellow atrophy of the liver was very definitely on the increase. The peculiar outbreaks such as were met with by Silbergleit and Föckler and at Cherryhinton Hospital were of course unprecedented ; but even apart from syphilis and salvarsan treatment, various writers have met with a quite undue number of cases of acute liver atrophy.

Umber (1920), for example, states that during the last five years he has seen ten cases of acute yellow atrophy, whereas in a previous period of eight years in Hamburg, he encountered four cases only. Of the first four cases seen in Hamburg, three were known to be in cases of syphilitic infection, but of the ten cases in the period of the war nine were certainly not syphilitic. He raises the question of the cause of this increase in acute yellow atrophy apart from syphilis, and his views will be referred to later on.

McDonagh (1918), referring to cases of syphilis only, states that, between 1906 and 1914, he met with only one case of acute yellow atrophy, occurring in a patient who had not been treated at all, whereas during the period of the war he has seen eight cases in patients treated with salvarsan.

Whether jaundice and acute yellow atrophy of the liver are more common nowadays than formerly is a problem attracting close attention in Germany. Two numbers of the *Medizinische Klinik* of last year (1921) contain the results of an ' Inquiry into the increased frequency of jaundice and acute yellow atrophy of the liver and the causes thereof '. The inquiry was apparently undertaken under the direction of Brandenburg, an editor of this journal, and a practising physician in Berlin. It was addressed to over twenty of the best known German physicians, among them Minkowski, Wechselmann, Krause, Krehl, Strasburger, Morawitz, v. Romberg, and v. Strümpell. Brandenburg has summarized the results of the inquiry, which may be briefly given as follows.

The need for the inquiry arose from the fact that in several places in Germany an obvious increase in the number of cases of jaundice and acute yellow atrophy had been noticed, and it was thought important to find out if this increase was general, or confined to certain localities. The results show that a definite increase in such diseases has occurred within recent times in certain large towns in North Germany, while in the south no such obvious increase is evident. In making the inquiry an opinion was also asked as to the probable cause of any increase noted, and the following direct question was set down for answer : ' Do you consider, from your

experience, that a connexion must exist between salvarsan treat-
ment and increased frequency of jaundice and acute yellow atrophy ? '
The answers to this question vary greatly, some being directly
affirmative, others as directly negative, while the majority, being
unable to give a satisfactory answer, merely discuss the possibilities
in more or less detail.

An additional point of interest emerging from the inquiry is that
two writers, who have met with an increase in hepatic disorders
after salvarsan treatment, definitely state that they believe these
ill effects to be due to too intensive treatment.

The data contained in this German inquiry relate chiefly to the
year 1920, and it is of interest in this connexion to consider
the number of disorders of the liver reported from civil venereal
treatment centres in England and Wales about the same time. The
main details of the latter are summarized in the following tables :

Number of cases of Syphilis treated during the year 1920.

	Males.	Females.	Totals.
New cases in 1920	28,799	14,006	42,805
Total cases under treatment	49,927	27,718	77,645

Number of cases of Hepatic Disorder.

Nature of ill effect.	Number of cases.	Number of deaths.
Jaundice—mild	18	0
,, moderate	4	0
,, severe	6	3
,, no particulars (probably mild).	10	0

It is thus obvious that the reports from civil treatment centres
with regard to both mild and fatal jaundice do not suggest, as far
as syphilitic infection and its treatment are concerned, any cause
for serious alarm in this country.

(g) Jaundice and Acute Yellow Atrophy of the Liver occurring in Munition Workers during the War.

During the war the subject of toxic jaundice and acute yellow
atrophy of the liver came into special prominence in connexion with
workers exposed to tetrachlorethane (' dope ' for aeroplane wings)
and trinitrotoluene (T.N.T.).

Tetrachlorethane was used as a solvent for acetate of cellulose,
and in workers employed in aeroplane construction was shown, as
early as the end of 1914, to be a powerful liver poison. Finally, on
the discovery of another solvent, the use of tetrachlorethane was
entirely abolished in 1916, but not before at least 70 cases of jaundice,
12 of which ended fatally, had occurred.

A full account of the effects of the trinitrotoluene is given in the
M. R. C. Special Report Series, Nos. 11 and 58, while the jaundice
and liver changes were fully discussed at a meeting of the Royal
Society of Medicine, 1917. During 1916 there were known to have
occurred 181 cases of toxic jaundice from T.N.T. poisoning, with
52 deaths.

In 22 post-mortem examinations the liver was always found

greatly diminished in size (17–36 oz.). The lesion was found to be a typical acute yellow atrophy, often with considerable secondary fibrosis, but with little evidence of regeneration on the part of the parenchyma. The morbid changes in the cases of poisoning with tetrachlorethane did not differ in any important respects from those described after trinitrotoluene.

In poisoning by these two substances, the conditions are of course very different from salvarsan administration, but there are certain important points in common. There is, for example, especially in patients suffering from the effects of trinitrotoluene, the similar occurrence of cases of severe jaundice, some of which pass on to acute liver atrophy, while the majority recover, just as in ' late jaundice ' following the administration of arsenobenzol preparations. In neither case has any real reason been discovered why some cases of apparently equal severity recover while others develop fatal acute yellow atrophy. Having regard to the views of Professor S. McDonald on the possible importance of bacterial infection, the known frequency of acute gastro-enteritis in chronic poisoning with trinitrotoluene must be mentioned.

A further important point of comparison with cases of salvarsan jaundice is brought out by three cases of delayed trinitrotoluene poisoning, referred to by Dr. W. J. O'Donovan (1918). In these cases the onset of jaundice occurred two months, six months, and ten months after all work with trinitrotoluene had ceased. The last case died with the lesions of acute yellow atrophy. These delayed cases of trinitrotoluene poisoning may be compared quite fairly with some of the instances of ' late jaundice ' following salvarsan administration referred to in a previous section (e. g. Pulvermacher's (1917) case—21 weeks, and Silbergleit and Föckler's case—103 days after cessation of treatment).

(*h*) Consideration of the diverse views held as to the relation of Arsenobenzol Compounds to the occurrence of Jaundice and Acute Yellow Atrophy of the Liver.

Before stating the conclusions of the Committee on this problem, it may be well to give extracts from the literature of the subject, to show the diversity of the views which have hitherto been held.

Citron (1919) believes that it is quite impossible to hold salvarsan in any way responsible for acute yellow atrophy in syphilis, because this complication, like other visceral manifestations of early syphilis, was well known in the pre-salvarsan era. He states that the same accusation was levelled against mercury, until Lebert described three cases in which mercury had never been employed at all. Citron compares the liver changes with those of another known spirochaetal disease (spirochaetosis icterohaemorrhagica), in which at necropsy no spirochaetes can generally be found, even with the most intense hepatic changes.

Fabry (1918) considers that jaundice appearing after salvarsan treatment must definitely be put down to fixation of the drug to the liver cells. He is of opinion that syphilis cannot be an aetiological

D

factor, since in all his cases of late jaundice the Wassermann reaction was negative, and all signs of syphilis were absent.

Milian (1920) is stoutly against the view that arsenic is the cause of the jaundice after salvarsan, and states that he can cure the jaundice by giving more arsenic, quoting two cases in favour of this thesis. Milian's views were put forward at a medical meeting, and were promptly opposed by Dufour and Sicard. Dufour pointed out that cases of mild jaundice quickly get better without any treatment at all, while Sicard expressed his strong belief in the toxic effect of the arsenic.

In consequence of his experience cited on p. 47, Umber (1920) is of opinion that the present frequency of cases of acute yellow atrophy has nothing to do with syphilis, and consequently is not due to arsenobenzol compounds. He agrees that, since Ewald in his book on hepatic diseases (1913) remarks that he did not see a single case in Berlin for fifteen years, the increased incidence must have some peculiar significance. He concludes that the frequency of acute yellow atrophy during the war is related to conditions quite apart from syphilis, and suggests that the faulty feeding induced by war conditions may possibly be blamed. His view is that an infectious cholangitis, arising from the intestine, plays a very important rôle in aetiology, and he quotes from recent publications of Naunyn on cholangitis, in which the same opinions are expressed.

McDonagh (1918) states that between 1906 and 1914 he only saw five cases of jaundice, and one of acute yellow atrophy, in syphilitic patients who had not been treated with salvarsan. In all of these the illness occurred in the early secondary stage, before the rash had fully developed. Since 1914 he has met with twenty-one cases of jaundice and eight of acute yellow atrophy after the administration of salvarsan. He concludes that acute arsenical poisoning is the basis of the trouble.

Pulvermacher (1917), in the course of a discussion on 'late jaundice', enters into the question of aetiology in great detail. He begins with some general considerations, and points out that the liver must be regarded as the main protective laboratory in the body. Not only does the liver destroy the products of intestinal putrefaction, but it has a similar function in the absorption of a number of chemical substances which may enter the body, e. g. alkaloids, metals such as iron, lead, copper and mercury, phosphorus, and, lastly, arsenic. He points out that Ehrlich during the course of the elaboration of the arsenobenzol compounds produced a preparation, later named ' icterogen ', having a very special action on the liver, with the production of intense jaundice. He argues that, while ' early jaundice ' may quite well be induced by arsenic, ' late jaundice ' must fall into another category, being dependent on individual peculiarities. In his view the salvarsan can only be an indirect or predisposing cause in the complicated aetiology of the hepatic disorders.

Rehder and Beckmann (1917), in a discussion on ' late ' jaundice, propound the following views. They believe that the liver, already damaged by the syphilitic virus, is unduly susceptible to arsenic, which sets up a catarrh of the bile ducts. In such a liver, various accidents—enteritis, alcoholism, the pregnant state, &c.—may bring

on jaundice of great severity, going on even to the condition of acute yellow atrophy.

Hallam (1920) thinks that it can now be definitely assumed that the use of arsenobenzol preparations is conducive to the production of jaundice during the treatment of syphilis, and states that hepatic disorder is more common after neosalvarsan than after the old preparation. He points out the occurrence in Sheffield of a series of cases of jaundice after many months of absolute freedom, and compares this outbreak with the fatal cases seen by Silbergleit and Föckler. He raises the question whether some infection resembling spirochaetal jaundice may not be the exciting factor of post-salvarsan jaundice.

Stokes, Ruedemann, and Lemon (1920) have published a striking series of figures relating to the curious incidence of jaundice in cases undergoing salvarsan treatment. In the Mayo clinic in America, approximately 5,200 patients were treated for syphilis between August 1916 and July 1920. Seventy of these patients became jaundiced (1·3 per cent.). The incidence of the jaundice was peculiar in that only six cases occurred between August 1916 and August 1918, whereas sixty-four cases were met with between August 1918 and August 1920. The methods of administration did not alter in any important respects during these periods. The writers suggest that the greatly increased frequency of jaundice in the second period is accounted for by infection, and is possibly connected with the great prevalence of epidemic respiratory disease at the time. One quarter of the cases of icterus gave a history of the known presence of jaundice in their locality, often in relatives, friends, or neighbours.

Professor Stuart McDonald's (1918) paper on acute yellow atrophy after salvarsan treatment has attracted great attention, chiefly from the results of the bacteriological examinations of the organs. It may be pointed out, however, that there was no evidence of bacterial infection during life. He suggests a prima facie case for regarding bacterial infection as the added factor which, acting on a liver previously damaged by syphilis and possibly also by arsenic and mercury, completes the damage of the hepatic cells.

E. Fraenkel (1920), in a discussion on the causation of acute yellow atrophy, reported that, among six cases, none of them connected with syphilis or salvarsan, he was able to isolate micro-organisms from the blood and bile on three occasions. It is to be noted that these bacteriological examinations were made after death. In two cases *Bacillus coli haemolyticus* was identified while the third case gave cultures of typical *B. paratyphosus* B. In all six cases the post-mortem appearances of the liver were quite characteristic. Influenced by these results, Fraenkel has come to believe that infection by micro-organisms is the essential cause of acute yellow atrophy, but that no single species of organism can be blamed.

It is obvious that little reliance can be placed on the bacteriological examinations referred to above, since they were carried out after death, and it is unfortunate that blood cultures have so seldom been made in cases of acute yellow atrophy during life. It is therefore important to refer to one unpublished case, reported to the

Committee by Sir Frederick Andrewes, in which blood cultures, carried out during life in a typical case of acute yellow atrophy, gave entirely negative results.

Turnbull (1920), in an investigation of the morbid anatomy of eight cases of fatal jaundice following salvarsan treatment, considers the question of the possible rôle of micro-organisms. In none of the eight cases were micro-organisms detected, except as terminal infections, and he points out how similar the hepatic lesion is to those induced by known exogenous poisons, such as trinitrotoluene. Ainley Walker (1920), in a research carried out for the Committee, has also shown that in rabbits the administration of salvarsan does not in any way prevent, but may actually appear to stimulate, the normal protective response to infection with micro-organisms, as measured by the production of agglutinins. (Cf., however, Moore and Keidel's views, p. 30.)

Frede (1920) considers that of all the suspected causes of jaundice and acute yellow atrophy in syphilis, none is so certain as salvarsan, although he admits that other accidental factors—gastro-enteritis, pregnancy, &c.—may operate locally or temporarily.

G. Herxheimer (1920) points out that the late effects of syphilis on the liver (gumma, &c.) have long been known, and he believes that we are now beginning to learn about the earlier manifestations. He emphasizes the absolute identity of the liver changes found in acute yellow atrophy in syphilis, whether salvarsan has been given or not, and supports the opinion of Milian that further treatment with arsenobenzol compounds does not increase the severity of the jaundice, but may have the opposite effect. He admits the possibility that late jaundice may arise from the arsenical drug setting up a catarrh of the bile ducts, but concludes that there is no reason at all to blame salvarsan for the occurrence of acute yellow atrophy of the liver in syphilis.

Foulerton (1921), in an article in which arsenobenzol is definitely accepted as a direct cause of acute yellow atrophy of the liver, suggests an interesting hypothesis as to the mechanism of the liver changes which occur in ' delayed poisoning ' after salvarsan compounds, trinitrotoluene, and chloroform. This is based on his belief that all these poisons are carried by, and combined with, the fats of the body. He considers that the delayed poisoning is due to the drug being fixed and gradually accumulated in the body fat, to be suddenly liberated and carried to the liver when, during any variation in the nutrition of the body, part of the fat is mobilized or set free for use in the body.

Turning for a moment to the literature concerning acute yellow atrophy in general, there seems to be no doubt that, excluding even special conditions, such as trinitrotoluene poisoning, jaundice and acute liver atrophy have been greatly on the increase during a period of time roughly corresponding to the salvarsan era, but still more closely corresponding to the period of the European War. This point has been sufficiently brought to notice in extracts from the literature already given in the report. Moreover, in the older literature of acute yellow atrophy, there is no indication that such remarkable outbreaks as occurred during the period of the war

(Silbergleit and Föckler, Cherryhinton Hospital, &c.) have been encountered at any previous time, though it must be remarked that jaundice is a common affection of troops under campaigning conditions.

In Germany at least, the increased frequency of jaundice and liver atrophy does not appear to have ceased with the end of hostilities, but, as is indicated in the inquiry directed by Brandenburg, still attracts great interest. It has been strongly suggested in Germany that the general ill nourishment of the population during the war must be an important disposing factor, although it is hard to see how positive evidence in favour of this view can be obtained. At a meeting of the German Pathological Society held in Jena in April 1921, Seyfarth (Leipzig) reported that between 1915 and 1920 there had been necropsies on twenty-three cases of acute yellow atrophy in the Pathological Institute at Leipzig, and that there was an increase in these cases corresponding with the return of the armies. He recognizes no single aetiological cause, but as disposing causes gives (1) fatigue of the populace after the war, (2) deficient nourishment, (3) syphilis, (4) abortion.

Lubarsch (Berlin), speaking at the same meeting, confirmed the increase in cases of acute yellow atrophy, and stated that syphilis and salvarsan had nothing to do with them.

On the other hand, Josselin de Jong remarked on the continued rarity of acute liver atrophy in a country which was not involved in hostilities, namely Holland.

It is interesting to note, while dealing with the conditions reported by German writers, that a small epidemic of jaundice has been reported by Todd (1921) as occurring in the British forces stationed on the Rhine since the armistice. The epidemic began in October 1920, and affected twenty-four men who had received treatment with salvarsan (' 914 '), and fifteen men who had never been treated with arsenic. One man suffering from syphilis and treated with salvarsan died of acute yellow atrophy of the liver five days after admission to hospital.

Todd has also, in a second and so far unpublished report, brought the results of his observations in the Rhine forces up to July 1921. In all, he personally has met with 53 cases of jaundice in syphilis treated with arsenobenzol compounds, during the period March 1920 to July 1921. In this time approximately 660 cases of syphilis had been under treatment, giving the quite unusually high incidence rate of jaundice of 8·3 per cent. No cases of jaundice were seen between March and October 1920, but all occurred after that date. During the same period (March 1920 to July 1921) 36 soldiers who had never received salvarsan treatment suffered from ' catarrhal jaundice ', among a military population of roughly 12,000.

(i) Temporary Hepatic Insufficiency following Administration of Arsenobenzol.

Quite apart from those cases in which hepatic insufficiency and damage are shown by the occurrence of obvious signs such as jaundice, evidence is gradually accumulating that a course of arsenobenzol

treatment is followed in practically every instance by a certain degree of hepatic insufficiency, not enough to give rise to active symptoms, and only recognized by special tests. Nevertheless, the recognition of a constant hepatic derangement is an observation which may finally assume great practical importance in stimulating research directed to the discovery of methods by which the liver cells may be protected against these arsenical drugs, and in directing and spacing out courses of arsenobenzol treatment.

The evidence has come from various sources, and especially from work carried out for the Committee at St. Bartholomew's Hospital by Dr. Mackenzie Wallis. This work, which will be published in full detail later on, may be briefly summarized here. Mackenzie Wallis has worked at the problem on similar lines to those which have yielded him results in the study of other conditions in which hepatic damage is well known to occur, namely, delayed chloroform poisoning and eclampsia. He points out the difficulties in investigating hepatic function by any single test, because of the multiple functions of the organ. Two tests have, however, yielded results of importance, namely the laevulose tolerance test, and the estimation of the lipase or fat-splitting ferment normally present in the blood. The laevulose tolerance test depends on the following principles. Normally almost all the sugar brought to the liver from the intestinal tract is converted into glycogen. Laevulose is a more suitable sugar to use than glucose for test purposes, since the liver is apparently the only organ in the body capable of dealing with laevulose. Briefly, the test as carried out by him consists in giving 25 grammes of laevulose by the mouth under certain defined precautions, and estimating the amount of sugar present in the blood at fixed intervals thereafter. This test of laevulose tolerance by estimating the sugar circulating in the blood was found to be of much greater value than the earlier method of giving 100 grammes of laevulose by the mouth and examining for an escape by the urine.

The test based on the lipase content of the blood depends on the fact that, in normal individuals, a fat-splitting ferment is present in remarkably constant amount. In conditions like eclampsia and chloroform poisoning, in which hepatic insufficiency exists, the blood lipase has been found greatly increased, even up to one hundred times the normal. This test has been employed, although less often than the laevulose tolerance estimation, in patients who have received a course of salvarsan treatment and has yielded similar indications of hepatic inadequacy.

The main results obtained so far by Mackenzie Wallis may be summarized as follows :

1. The effects of one or two injections of arsenobenzol preparations are almost always very slight, and little evidence of hepatic damage may be found at the end of a course of six injections.

2. The most striking results are obtained when the tests are applied three months after the last injection. Evidence of hepatic insufficiency is then detected almost invariably, although no clinical signs of hepatic disorder may be discovered.

3. Six months after the last injection all evidence of hepatic

insufficiency has gone, in cases where three months before it was clearly shown by the tests.

It is obvious that the importance of these findings, if widely confirmed, may be very great in connexion with the safe spacing out of courses of arsenobenzol treatment.

Spence and Brett (1921) have independently investigated the effects of injections of arsenobenzol compounds on the function of the liver, making use of the laevulose test only. Their results, which refer especially to cases of jaundice following arsenical treatment, have been published in full, and may therefore be summarized quite briefly. In every patient suffering from jaundice following injections of arsenobenzol, insufficiency of the liver was demonstrated in varying degree. In a fatal case, an extreme degree of functional disturbance was indicated by the test, and at the necropsy severe degenerative lesions of the liver were found. These writers did not specially investigate cases in which arsenobenzol treatment appeared to be well borne, and in which no jaundice supervened. They refer, however, to one case of tabes dorsalis, treated with arsenobenzol up to within three weeks of the test being applied, in which a slight degree of hepatic insufficiency was shown to exist by the laevulose test. A summary of further work by these writers has been communicated to the Committee by Colonel L. W. Harrison. They have now clearly shown that a deleterious effect on the liver may be demonstrated by the test in patients who have received only one or two injections of arsenobenzol, this being in fair agreement with the results of Mackenzie Wallis.

Widal, Abrami, and Iancovesco (1920) have used for the same purpose of estimating hepatic insufficiency, the so-called ' Épreuve de l'haemoclasie digestive ', introduced by Widal in 1920. This test is as yet insufficiently controlled by others to permit us to appraise its permanent value. These authors, who give the details of the test, have found evidence of hepatic insufficiency without jaundice or other overt signs, 18 and 24 days after the end of a normal course of salvarsan treatment. In another case, treated more intensively, hepatic insufficiency was still found to exist four months after the last injection of arsenobenzol. Further, in four cases of ' late jaundice ', coming on 17, 25, 32, and 45 days after all treatment had ended, the test strongly indicated hepatic insufficiency in all.

The haemoclasic reaction of Widal (a full description of which is given in the article by Widal, Abrami, and Iancovesco) has been carried out by Todd in seven cases of jaundice following arsenobenzol treatment, occurring among British troops on the Rhine. This report is as yet unpublished, and the Committee are indebted to Major Todd for the details. In six cases the test was positive, while in one case with definite icterus it was negative. Todd also reports an additional case of jaundice in which a negative result was obtained, but in which the later history ' left no doubt that a condition of hepatitis was present '.

VII. TWO OUTBREAKS OF SEVERE ILLNESS FOLLOWING ADMINISTRATION OF ARSENOBENZOL COMPOUNDS IN BRITISH MILITARY HOSPITALS

During the year April 1917 to April 1918 certain military hospitals exhibited a peculiarly high incidence of fatal jaundice following the use of ' 606 ' or ' 914 ' in the treatment of syphilis. These outbreaks indeed were largely responsible for the establishment in 1918 of the Salvarsan Committee.

In four centres in particular, viz. Newcastle, Dublin, Cambridge, and a Canadian military hospital, the number of fatalities within a comparatively short period was large enough to attract particular attention. Reports have been published by Stuart McDonald and by Strathy, Smith, and Hannah on the outbreaks at Newcastle and at the Canadian military hospital, and these are referred to in the review above (pp. 38 and 42).

Through the kind offices of Colonel Harrison, the Salvarsan Committee have obtained a large amount of information about the outbreak of jaundice at the Cherryhinton Hospital and about the peculiar group of cases at the Portobello Military Hospital, Dublin, and they have devoted much time to a careful study of the available facts with the object of coming to a conclusion as to the causes which led to the ill effects in these instances.

(a) Outbreak of severe Illness among cases of Syphilis at the Central Hospital, Portobello Barracks, Dublin.

During the two years preceding November 1917 about 10,000 injections of salvarsan had been given to cases of syphilis treated at the Military Hospital, Portobello, with no untoward incidents beyond the usual reactions in a proportion of the cases. Between November 21 and December 28, 1917, a series of patients presented unusual symptoms ending fatally in a large proportion of the cases. The Committee have studied the records of fourteen patients treated at this hospital during the period in question who suffered from ill effects. Of these fourteen, one fatal case had received no arseno-benzol treatment in the Portobello Hospital, but had previously been under treatment for syphilis in Cherryhinton Hospital, Cambridge. His case is referred to in the account of that outbreak (No. 22, B.W.P.). Two other cases presented symptoms differing from those observed in the remaining cases. One (H.) was a case of ordinary mild catarrhal jaundice ; the other was a case of acute arsenical dermatitis. Both of these recovered. Excluding these three there were eleven cases in the peculiar outbreak, and of these nine died ; the case mortality was therefore very high—nearly 82 per cent.

The Committee are greatly indebted to Professor A. C. O'Sullivan for his courtesy in supplying information on these cases, and on the results of post-mortem examination, and for copies of reports on the patients by other medical officers concerned.

Clinically these cases showed sudden onset of great weakness and prostration : fever varying from 100°–103° F., ; jaundice of varying

degree but never very deep ; dusky, rather cyanosed facies ; albumin and bile in the urine ; feeble pulse ; profuse sweating. Absence of vomiting and diarrhoea. Consciousness and mental clearness were retained often up to the time of death.

Necropsies were made by Professor O'Sullivan in six cases (Nos. 1, 2, 6, 7, 10, 11 in tables). The post-mortem appearances were very similar in all.

Spleen. Enlarged, deep red, almost black in colour ; firm but friable, showing irregular nodules bulging on section.

Liver. Enlarged (up to 5 lb. 1 oz.), soft and friable, dark brown with a bluish tinge, full of blood.

Kidneys. Somewhat enlarged, greyish red, and flabby.

Brain. In one case slatey grey in colour (No. 1).

Pancreas. Slatey grey in three cases.

No pronounced lesions found elsewhere.

Petechial haemorrhages in serous membranes and varying degree of jaundice.

Faeces deeply stained with bile ; the common bile duct was patent. Gall bladder in several cases distended with dark, thick bile. In one case (No. 6) it was empty.

Serous membranes contained varying amounts of clear yellow fluid ; in one case only were they dry. The brain showed in most cases an accumulation of fluid under the pia-arachnoid and in the ventricles.

No lesions in intestines.

Lungs oedematous in posterior and lower parts, and emphyse-matous, as a rule, at the anterior margins. Only two cases showed any evidence of syphilis. In these there was a specific aortitis, and in addition granular kidneys.

Histological examination of tissues (Cases 1, 6, 7, 11). Parasites of malignant tertian malaria were abundant in the internal organs (kidneys, liver, spleen), the capillary vessels contained numerous malignant tertian parasites, some within the red corpuscles, others free. The tissues, stained with Leishman's stain, showed the bodies of the parasites of a light blue colour containing a small mass of dark pigment in their interior. The chromatin was not stained. In a few cases the parasite was found in a state of commencing sporulation. Speaking generally, all the cases showed an intense pigmentation of liver and spleen, especially the latter. In the case of H. J. T. (No. 1) the pia mater was also pigmented, and the capillaries of the brain were packed with parasites, many of them in a state of sporulation. The pigment was almost black and lay in the inside of the parasites, or free in small masses of the same size and appearance as those in the parasites, or was collected in clumps in large cells. In the spleen the pigment and parasites lay entirely in the pulp ; in the liver they lay either in the capillaries or between them and the liver cells. The liver cells themselves rarely contained any pigment. The cells which took up the pigment were, when recognizable, either endothelial cells or leucocytes. The tissues also showed varying degrees of fatty change, especially the heart, liver, and kidneys of patients 1 and 6.

TABLE VII. Portobello Hospital Cases.

No.	Initials.	Age.	Service.	Date of admission.	Barrack room.	Salvarsan (kharsivan). Date of first injection.	Salvarsan (kharsivan). Date of last injection.	Date of Onset of illness.	Date of Death.	Remarks.
1	H. J. T.	22	6/12	1. 8.17	12 D	29.10.17	10.12.17	20.12.17	8. 1.18	Diagnosis of malaria from blood drawn from spleen.
2	R.	50	2 2/12	17. 9.17	16 D	29.10.17	17.12.17	31.12.17	4. 1.18	No particulars.
3	P. D.	30	17	17.10.17	13 D	22.10.17	12.11.17	16.11.17	25.11.17	
4	F. McG.	38	19 1/12	20.10.17	.	22.10.17	19.11.17	26.11.17	Recovered	Jaundice. Never seriously ill.
5	D.	31	3 3/12	2.11.17	13 D	5.11.17	17.12.17	26.12.17	26.12.17	
6	T. McK.	28	3 1/12	5.11.17	6 D	12.11.17	24.12.17	2. 1.18	6. 1.18	
7	J. H. J.	26	1 1/12	5.11.17	14 D	12.11.17	18.12.17	1. 1.18	6. 1.18	Jaundice.
8	A. R. P.	39	1	7.11.17	2 B	19.11.17	(? 17.12.17)	4. 1.18	Recovered	
9	McD.	21	3	10.11.17	16 D	12.11.17	17.12.17	...	26.12.17	Jaundice.
10	J.	37	1 1/12	22.11.17	13 D	3.12.17	17.12.17	27.12.17	2. 1.18	
11	A. M. C.	30	3	13.11.17	8 B	19.11.17	24.12.17	5. 1.18	6. 1.18	

TABLE VIII. Portobello Hospital Cases. Treatment with Arsenobenzol Compounds and Mercury.

No.	Initials.	Dates of injections.	Salvarsan. Batches (kharsivan).	Salvarsan. No. of doses.	Mercury.	Result.	Remarks.
1	H. J. T.	Oct. 29 ; Nov. 5, 12, 19, 26 ; Dec. 3, 10, 1917	598 367 600	7	9 injections	Died	
2	R.	Oct. 29 ; Nov. 5, 12, 19, 26 ; Dec. 10, 17, 1917	598 600	7	7 injections	Died	No jaundice.
3	P. D.	Oct. 22, 29 ; Nov. 5, 12, 1917	598 600 367 (?)	4	3 injections	Died	Icteric tinge during life.
4	F. McG.	Oct. 22, 29 ; Nov. 5, 12, 19, 1917	598 600	5	4 injections	Recovered	Liver and spleen enlarged. Malaria diagnosed by blood exam.
5	D.	Nov. 5, 12, 19, 26 ; Dec. 3, 10, 17, 1917	?	7	?	Died	No information.
6	T. Mck.	Nov. 12, 19, 26 ; Dec. 3, 10, 17, 24, 1917	598 600	7	7 injections	Died	Not jaundiced.
7	J. H. J.	Nov. 12, 19, 26 ; Dec. 3, 10, 17, 1917	598 600	6	4 injections	Died	Skin slightly yellow.
8	A. R. P.	Nov. 19, 26 ; Dec. 3, 10, 18, (? 17), 1917	598 600	5	4 injections	Recovered	Jaundice for some weeks. Malaria crescents found in blood.
9	McD.	Nov. 12, 19, 26 ; Dec. 3, 10, 17, 1917	598 600	6	5 injections	Died	Slight icteric tinge of skin.
10	J.	Dec. 3, 10, 17, 1917	599 600	3	4 injections	Died	
11	A. M. C.	Nov. 19, 26 ; Dec. 3, 10, 17, 24, 1917	598 600	6	6 injections	Died	Jaundice.

Bacteriological examination of blood and fluids taken from the bodies gave negative results. The tissues of Cases 7 and 10 were tested for arsenic. but none was found. Traces of arsenic were found in the urine of Case No. 10.
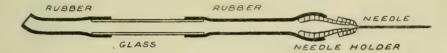
No necropsy was obtainable in the case of patients P. D. and McD. (3 and 9). The information as to No. 5 is rather scanty. This patient died, but no post-mortem examination was made. Clinically, his case is said to have been similar to the others.

An Army Committee appointed to consider the outbreak reviewed the evidence and came to the conclusion that it was due to infection with malaria.

The cases affected occurred in a group within a period of seven weeks. They received their injections on Mondays during the period October 22 to December 24, 1917. About thirty men were injected at Portobello every day. The injections were usually given at weekly intervals, and each man received his weekly injection on the same day of each week.

In making the injections the practice was as follows :

There was a short india-rubber tube at one end of which was a metal adapter for the attachment of the injection needle. The

RUBBER   RUBBER   NEEDLE

GLASS   NEEDLE HOLDER

metal adapter had a bulbous base over which the india-rubber tube fitted. The other end of this short india-rubber tube was fitted on to a piece of glass tubing about three inches long, and this again into a long india-rubber tube leading from the receptacle holding the solutions. When the needle was inserted into the vein the blood was allowed to run back into the short glass tube so as to make sure that the needle was in the vein. The solution was then let in, and the blood was to a great extent washed out of the tube, but at times some remained visible in the tube. There can be little doubt that blood was also retained between the bulbous adapter and the india-rubber tube, the shape of the section being somewhat as here indicated. The needle was changed for each case, but not the adapter or the short india-rubber or the glass tubes.

The symptoms developed usually within a fortnight after the last injection of ' 606 '. The presumption arrived at by the Army Committee was that the men were infected with malaria from the blood of other patients by direct transfusion of a small quantity of blood remaining in the tube. The grave nature and high fatality of the cases might be explained on this supposition, since ' the dose of parasites received was probably a very large one '.

No examination of the blood of these fatal cases was made for *malarial* parasites during life, as at first the symptoms were thought to be due to arsenobenzol poisoning or to spirochaetal jaundice.

With regard to the past history of those affected, it is to be noted that only A. R. P. (Case 8) was known to have been in a malarial area. He had been to Greece and to other Mediterranean ports as

steward on board a ship. Some of the men had never been out of the British Isles, the others no further afield than France. Crescents were found in the blood of A. R. P. and F. McG. (Cases 8 and 4), the two survivors. In addition to A. R. P. (Case 8), who may have been the malaria carrier, and who is known to have suffered from malignant malaria, two other men (not included in this series) were known to have had malaria, and were undergoing salvarsan treatment at the time. The Salvarsan Committee have no information as to the precise dates on which these two men received salvarsan injections, but it is known that they were injected on Mondays, i. e. the same day of the week as the sufferers. It is not known whether these men had the malaria parasite in their blood at the time, nor by which species of malarial parasite they had been infected.

TABLE IX. *Military Hospital, Portobello. Showing Dates on which Patients were Injected with ' 606 '.*

Dates of injections.	Identification numbers of cases injected on any one date.							
22.10.17	3	4	..	..	..	..	..	..	..
29.10.17	3	4	1	2	..	..	..	..	..
5.11.17	3	4	1	2	5	..	..	..	..
12.11.17	3	4	1	2	5	6	7	9	..
19.11.17	4	1	2	5	6	7	8	9	11
26.11.17	1	2	5	6	7	8	9	11	..
3.12.17	1	5	6	7	8	9	10	11	..
10.12.17	1	2	5	6	7	8	9	10	11
17.12.17	2	5	6	7	8	9	10	11	..
24.12.17	6	11	..	..	..	..	..	..	..

Note.—Every case, except Case 3, had one or more injections on the same date as Case 8.

This Portobello outbreak is one of anomalous type, and very interesting: It is clear that death took place from malaria, and that arsenobenzol preparations were not directly concerned.

The evidence is not complete as to infection by means of transfusion of blood by the apparatus used in injection of ' 606 ', inasmuch as there is no information as to the order in which the injections were given on the various dates in Tables VIII and IX to the patients tabulated therein. It will be noted, however, that Case 8 (A. R. P.), who was known to have had malignant malaria, came into association (by injections given on the same date) with all the cases except No. 3. The fact that No. 3 had no injections on the same dates as No. 8 suggests that, if the explanation given above as to infection by transfusion of blood is correct, there must have been another malaria carrier in addition to A. R .P.

The Committee considered the question of the possibility of indigenous malaria in connexion with these cases. Ireland was at one time supposed to be very free from malaria, but Wylde, in 1841, refers to the fact that tertian had become common, possibly by introduction by labourers from the fen countries. Dr. Tuomy, in 1810, stated that during autumn, winter, and spring some sporadic cases are commonly observed every year in Dublin, especially under a quotidian form. A big epidemic occurred in 1805, also in 1809. Stokes referred to an outbreak in 1829.

The map showing the known distribution of the *Anopheline mosquitoes*, published by W. Dickson Lang in 1918, indicates that *Anopheles maculipennis* had been found in various parts of Ireland, also *Anopheles bifurcatus* and *Anopheles plumbeus* Stephens. In England, several outbreaks of indigenous malaria have been recorded in recent years owing to our native mosquitoes becoming infected with malaria from soldiers returning from malarious countries.

With the exception of two cases recorded in 1920 no indigenous case of malignant tertian malaria is known to the Committee to have been recorded in England. It would seem, moreover, difficult to explain the Portobello outbreak on the hypothesis of an indigenous malaria, bearing in mind its limitation to a small group of men all suffering from syphilis, and all under treatment by ' 606 ', and that the cases occurred at a period of the year when such cases do not arise *de novo* in this country.

As regards the hypothesis of infection by transfusion of blood, Gerhardt (1884) produced malaria by injection of quotidian blood (' a Pravaz syringe full '), the incubation period being seven days in one case and twelve days in another. Elting (1898–9), working with Thayer, experimented with benign and malignant tertian by intravenous or subcutaneous injection of blood. The amount injected was 1·5–4 c.c. Of four inoculated with tertian there were two positive and two negative results. With summer–autumn infection six people were inoculated, all with positive results. It is stated that two or three drops of blood containing summer–autumn parasites injected subcutaneously can produce an experimental infection.

Following Wagner von Jauregg's suggestion that persons suffering from general paralysis are improved by an intercurrent febrile attack, Mühlens and Kirschbaum (1921) have experimentally injected malarial blood into patients suffering from G.P.I., blood from cases of tertian, quartan, and tropical malaria being employed. The defibrinated blood was injected subcutaneously in doses of $\frac{1}{2}$ to 1 c.c. Later, whole blood was injected in doses of $\frac{1}{4}$ to 1 c.c., although the smaller dose frequently failed to establish infection. Of great interest is the fact that indigenous specimens of *Anopheles maculipennis* (from Cuxhaven), allowed to suck the blood of a patient artificially infected with tropical blood, showed a development of parasites up to the sporozoit stage at 23° to 25° C. in January.

It may be of interest to refer to the case reported by F. Glaser (1921), in which a latent malaria was lighted up by administration of salvarsan preparations. The patient (a male, aged 28) acquired syphilis in January 1921. On February 7, he received 0·15 gm. neo-salvarsan, and on February 12, 0·3 gm. He had mercury also on three occasions. Fever set in with pains all over the body, and he took to bed for eight days. After recovery he received seven injections of sodium salvarsan (no doses stated), but no more mercury. The last salvarsan injection was given on March 19, 1921. Two days later he had rigor, fever, sweating, pains in joints, and at the end of the month yellowness of skin. On March 31 he was admitted to hospital with well-marked jaundice, enlarged spleen, but with liver of normal size, and died on April 3. Post-mortem : he was found to

have died from malignant jaundice. There was universal icterus. The spleen was full of black pigment. There was an enormous quantity of pigment in the bone marrow. The reticulo-endothelial tissue of the liver was loaded with pigment, and there was well-marked swelling and proliferation of Kupffer's star cells.

In the Portobello outbreak it is difficult to account for the cases on the theory of transfusion of blood, except on the assumption that, under some conditions, extremely minute amounts of blood may produce fatal infection.

In any event the occurrence suggests the desirability of taking suitable precautions, in connexion with the technique of injections, to prevent the possibility of transference of blood from one patient to another by the apparatus used for the injections.

(b) Outbreak of Jaundice in Cases treated at Cherryhinton Military Hospital, Cambridge.

Particulars were furnished to the Committee with regard to 39 patients who had been treated at the Cherryhinton Hospital, Cambridge. After careful consideration the Committee rejected two cases as not being suitable for inclusion in the series. Information about these two cases was probably supplied because the patients had been in Cherryhinton Hospital during the period of the outbreak and had subsequently died.

One of these patients, who contracted syphilis 18 years previously in India received no treatment by arsenobenzol compounds whilst in the Cherryhinton Hospital but had merely one dose of Mist. Pot. Iod. (5 grains). He was admitted to the hospital with laryngeal dyspnoea on October 14, 1917, and died on October 31. There was no evidence of jaundice during life. The other case presented greater difficulties. He was admitted on July 9, 1917, with enlarged inguinal glands and an infected throat. There was a history of syphilis in 1905, for which he had received four months' treatment. Whilst in Cherryhinton Hospital he had 10 injections of arsenobenzol compounds, receiving in all 3·7 gm. kharsivan and 0·3 gm. arsenobillon. He had also 11 grains mercury and was treated for 14 days with Mist. Pot. Iod. Six days after discharge from hospital to his unit he was put on guard, but felt ill and was relieved. He died the following day.

Post-mortem. Pneumonic consolidation of both lungs was found. There was no evidence of jaundice. The Committee came to the conclusion that this must be regarded as a death from pneumonia, without any connexion with the previous treatment.

Excluding these two cases, there were 37 cases of men treated in the Cherryhinton Hospital during the period February 1917 to April 1918 who developed jaundice during or after administration of ' 606 ' or ' 914 '. By far the larger proportion of the cases occurred between August and December 1917, so that the outbreak presented something of an explosive character (see Chart I).

The Cherryhinton Hospital was established in 1916. It had accommodation for 866 patients, 90 R.A.M.C. orderlies, and 23 sergeants. It was arranged in five lines of huts : A, B, C, D, E (see plan).

Line E (9 huts) was reserved for gonorrhoea cases. Lines A and B were used for syphilis (Huts 2 to 8 in each line). Lines C and D were used rather as overflows from A and B lines, and only 11 of the 18 huts in these two lines appear to have been occupied by patients. Between lines A and B were latrines and ablution huts; similarly between C and D. Latrines, &c., for line E were placed to the left of that line.

During the period the Cherryhinton Hospital was open (from 1916 to 1920), 8,589 cases of syphilis were treated with arsenobenzol compounds. Between February 1, 1917, and February 28, 1918, 2,933
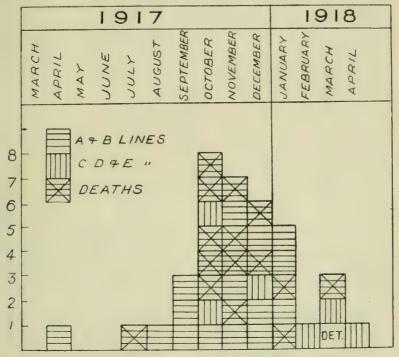
CHART I.—Showing Hut incidence and month of onset of 37 Cherryhinton cases.

new patients suffering from syphilis were admitted and treated with arsenobenzol compounds.

The number of cases of jaundice (37) was therefore unusually large in proportion to the total number of cases of syphilis under treatment during the period covered by the outbreak.

The first case of the series under consideration (No. 13) commenced with jaundice on April 9, 1917. The next case (No. 1) did not develop jaundice until July 16, 1917. The last case (35) began to be ill on April 6, 1918, and was jaundiced the following day. The largest block of cases occurred in October and November 1917 (see Chart I). The interesting information was received from the Medical Officer of Health of Cambridge that during the autumn of 1917 there was a small outbreak of catarrhal jaundice among the children of an elementary school in the Cherryhinton District, affecting 15 children

and one adult. There is also evidence that there were several other cases of jaundice in children distributed about that period in and around the town of Cambridge. There were apparently no fatal cases. Out of the 37 military cases mentioned above there were 15 fatalities. All the cases had been under treatment for syphilis with arsenobenzol compounds and with mercury. Particulars as to the dates of injections, the dosage, and the preparations used will be found in Table XI.
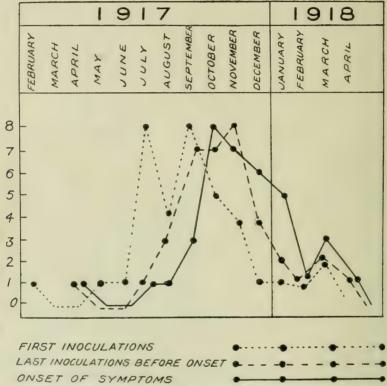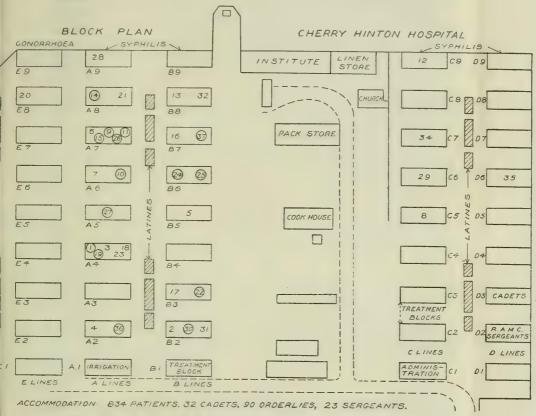
CHART II.—Showing for each month the number of first injections, the number of last injections before onset of symptoms, and the number of cases in which symptoms first appeared during the month.

Five of the fatal cases and two of the non-fatal cases had, in addition, received treatment with arsenobenzol preparations prior to their admission to Cherryhinton.

As cases of spirochaetal (icterohaemorrhagic) jaundice had occurred in France, examinations were made at Cherryhinton of blood from a considerable number of patients, and it is stated that in one case a single spirochaete was found. The description given of this did not correspond with *Sp. icterohaemorrhagiae*, and injections into guinea-pigs gave negative results. In view of the failure to infect guinea-pigs the Committee, after careful consideration of all the available data, are not inclined to attach any importance to this observation.

The cases can be grouped into two main types:

(a) Those in which jaundice alone or jaundice with malaise and gastro-intestinal disturbances were the only symptoms. These cases recovered more or less rapidly, and in six instances, after recovery, further intramuscular or intravenous injections of arsenobenzol preparations were given without a recurrence of the previous symptoms.

(In this plan the numbers shown inside the rectangles representing individual huts are the identification numbers of patients referred to in the text. The numbers relating to patients who died are enclosed in circles.)

(b) Those in which jaundice was associated with severe prostration, vomiting, pains in abdominal, costal or lumbar regions, and delirium sometimes succeeded by coma. These cases were predominantly fatal.

The outbreak showed marked predilection for A and B lines in the hospital (see plan), where all the severe and fatal cases occurred.

Main details as to the clinical features.

Jaundice. Of the 22 non-fatal cases, 14 were of a mild nature, jaundice or jaundice associated with some malaise being the only symptoms. The remaining 8 cases showed jaundice with a certain amount of vomiting and gastro-intestinal disturbance.

6022   E

In only two or three of the cases is there positive evidence, e. g. mention of clay-coloured motions, that the jaundice was of an obstructive type.

With respect to the 15 fatal cases, 14 of these had jaundice of varying intensity noted during life. In all these cases jaundice was the first or one of the earliest symptoms recorded. In the remaining case (No. 19) jaundice was recorded at necropsy only.

Pyrexia. In only 3 or 4 of the cases is a definite rise of temperature (over 100° F.) recorded. Several of the cases, however, were rapidly fatal. Towards the end the temperature was often subnormal.

Gastro-intestinal disturbance. Mainly vomiting and diarrhoea. In one case definite haematemesis is mentioned, and in one case vomiting of ‘ dark fluid ’. Pains occurred in about 10 of the 23 more severe cases, mainly over the epigastric regions ; also over the right costal and lumbar regions. In one case mention is made of pain in the legs as well as over the stomach.

Herpes of lips is mentioned in one case (No. 37).

Urine and blood changes. Examination of blood was carried out in certain cases after the onset of jaundice. The following is a summary of the results :

Case.	Identi-fication number.	Number of		Haemo-globin.	Character of W.B.C.
		R.B.C.	W.B.C.		
J. S.	24	4,200,000	17,000	70 % 65 %	70 % polymorphonuclears. 28 % lymphocytes. 2 % transitionals and small mono-nuclears.
E. H.	25	3,750,000	13,800	65 %	59 % polymorphonuclears. 35 % lymphocytes. 4 % transitionals. 1 % basophils.
G. H. D.	26	..	20,000	..	81 % polymorphonuclears. 14 % lymphocytes. 4 % transitionals and large mono-nuclears. 1 % basophils.
J. A. C.	31	..	16,000	..	69 % polymorphonuclears 27 % lymphocytes. 3 % transitionals and large mono-nuclears 1 % basophils.
D. C.	37	Had a polymorphonuclear leucocytosis.			

Notes on the URINE are available in the following :

J. S.	(24)	Deep red ; albumin present, casts and bile.
E. H.	(25)	Contained bile ; trace of albumin, with casts.
G. H. D.	(26)	Acid, 1,028 ; albumin, + + ; no sugar ; trace of bile. A few w.b.c. and crystals. No casts.
J. A. C.	(31)	Non-fatal case but of same type. No albumin, casts, or bile.
J. E. C.	(36)	Dark amber; acid, 1,016 ; albumin, + + ; pus, + + ; granular casts, + +.
E. W.	(32)	Non-fatal case, apparently of same type ; ‘ nothing abnormal found in urine.’

Pathological Appearances in fatal Cases.

These comprised presence of blood in stomach and intestines ; multiple subserous haemorrhages especially in the abdomen.

Liver. In ten instances the liver was reduced in size, in three it was stated to be normal in size, and in one slightly enlarged.

Microscopical specimens of the liver showed some variation in individual cases, but generally there was evidence of increase of connective tissue, degeneration of the liver cells, and cellular infiltration. A detailed description of the microscopical appearances in certain of the cases will be found in the report by Professor Turnbull recently published (Reports of the Medical Research Council. Special Report Series, No. 55).

Interval between Date of last Injection of Arsenobenzol and Onset of Symptoms. (See Tables XI and XII.)

In the 22 non-fatal cases this interval showed great variation. (See table below and XII(b).)

Onset of symptoms occurred.	Non-fatal cases.	Fatal cases.	Total.
On day of last injection, or following day	4	..	4
2 days after last injection	2	..	2
3 days after last injection	4	1	5
3–7 days after last injection.	4	1	5
7–21 days after last injection	4	2	6
Over 21 days after last injection	4	11	15
	22	15	37

The onset was delayed up to 57 and 84 days in two non-fatal cases ; in the fatal cases the longest interval was 56 days.

The interval between the onset of symptoms and death was very short in 12 of the cases (eight days or under). In 4 of the cases death ensued 1 day after onset of symptoms. In the three most protracted cases the interval between onset and death was 11 days, 11 days, and 31 days.

Cases which call for special Remark.

Some particulars of all the 37 reported cases are given in the tables in the appendix. Two cases, however, require special mention.

Case 12 (W. N.), Hut C, 9. This case, of mild jaundice occurring 3 days after the last injection, is said to have had, during the previous 12 months, relapsing attacks of jaundice, the first occurring whilst he was in the Gallipoli Peninsula. It is perhaps doubtful if this case can be rejected, but it is at least possible that this was simply a recurrence of the previous attacks.

Case 22 (B. W. P.). This patient was discharged from Cherryhinton on December 1, 1917, after the arsenobenzol course. He was admitted to Portobello Hospital, Dublin, about the end of December, but had no treatment there. On January 11, 1918, he was transferred to King George V Hospital, Dublin, with some jaundice, weakness, and restlessness. He died on January 14, 1918. The post-mortem appearances differed somewhat from those in the other Portobello cases, e. g. spleen and liver did not show the enlargement noticeable in the other cases (see p. 57), the liver weighing only 41 ounces.

Microscopically no malarial parasites were seen, but pigment was present in large quantities in the spleen, liver, and in the muscle cells of the heart. The pigment was black in colour, and in the form of small round globules. There was intense fatty degeneration of heart, liver, and kidneys.

Through the courtesy of the War Office the Committee were able to study the medical history sheets of this man. He enlisted in February 1907, at the age of 18 years and 2 months, and went to India in 1909. He was admitted to hospital in Jubbulpore in 1909 with gonorrhoea. In 1910 he was admitted to hospital with 'malaria', the parasite of benign tertian being found. He was admitted to hospital in Calcutta in December 1914 for 'malaria' (malignant). In 1916 he suffered from ulcer of the leg and syphilis, with a positive Wassermann reaction. He received 2·8 grammes '606' at Hilsea Hospital, and was discharged as free from active syphilis. In March 1917 he was found to have a large sore on the penis, and ultimately was sent to Cherryhinton on September 4, 1917.

The history of malaria in India sufficiently explains the appearance of pigment in the tissues noted post-mortem. These appearances were evidently due to a malaria of much older standing than could be explained by any infection acquired in Portobello Hospital.

As this patient did not receive any treatment in Portobello Hospital, but had been treated in Cherryhinton Hospital, and as the post-mortem appearances indicated that death was the result of acute atrophy of the liver, as in other Cherryhinton cases, it seems clear that this case should be differentiated from the Portobello group, and classified with the other Cherryhinton cases as one of acute yellow atrophy.

Details of the Outbreak with special Reference to Hutment Incidence.

Reference to the plan shows that, of the 37 cases reported, no less than 30 occurred in adjacent lines A and B, the heaviest incidence falling on A. All the fatalities occurred in patients who had lived in A and B hutments. All the cases in C, D, and E lines were mild cases of jaundice. Further, while the onset of the first case in the Cherryhinton Hospital commenced in Hut B 8 on April 9, 1917, the date of onset of the first case in C and D lines was not until October 13.

In the month of October there were two cases in C lines, including Case No. 12 (the case of recurring jaundice referred to on p. 67). There were no further cases in C and D lines until February 1918 (1 case). One case occurred in March 1918 in C and D lines, and 1 case in April 1918 (the last of the series). The one case in line E occurred in December.

Details of the First Case in the Hospital and subsequent Course.

The first case occurred in Hut B 8 (case 13). This man (aged 31) was admitted on February 6, 1917. He received his first injection on February 17, and his last injection on April 4. The onset of jaundice was on April 9. He recovered, and was discharged on April 23, sixteen days before the second case in order of onset was admitted to the hospital for syphilis.

The second case (No. 1, Hut A 4) developed symptoms on July 16, i. e. over three months subsequent to the onset of the first case. This case ended fatally.

The onset of the third case (No. 2, Hut B 2) was on August 15. Three cases occurred in September, 8 in October, 7 in November, 6 in December, 5 in January 1918, 1 in February, 3 in March, and 1 in April, which was the last of the series.

Summary

In all there were 37 cases, 15 of which were fatal. All these patients had arsenobenzol compounds. A large majority of the cases, and all the fatal cases, occurred in patients treated in huts on one side of the camps (see Hutment Incidence above). Conditions were much the same on the two sides of the camp, except that a much larger total number of cases of syphilis were treated in lines A and B than in lines C and D. The treatment room was different for the two sides of the camp, and the injections were given by different doctors, but the same batches of ' 606 ' and the same re-agents were used, and the ' 606 ' was prepared by the same individual for both treatment rooms. Some patients had kharsivan, other had arsenobillon or novarsenobillon, and two had galyl. It was notable that in some cases a considerable period of time elapsed between the last dose and the appearance of symptoms.

The outbreak came to an end spontaneously, without any apparent change in method. The whole outbreak occurred between March 1917 and April 1918. The first case occurred in March, but it was not until July that the next case occurred. There was no evidence implicating any particular brand of arsenobenzol preparation or any particular part of the technique. There were practically only two brands used.

(c) Note on the Batches of Arsenobenzol Compounds used at Cherryhinton during the Period of the Outbreak.

The question arises whether the occurrence of the group of cases of toxic jaundice can be associated with the use of abnormally toxic preparations. It may be stated at once that an examination of the records of the batches of kharsivan and arsenobillon used in treating these cases gives no definite support to this view.

There is evidence of some inaccuracy in the recording of the batches of material used. Thus numbers occur, corresponding to batches which failed to pass the official test, and the Committee are satisfied, after inquiry, that batches bearing these numbers were never, in fact, issued for use. Other numbers do not correspond to any batches which have ever been submitted for test, and some of these were far beyond the range of numeration which had been reached for the preparation in question at the date of the recorded use. There is no room for doubt that these entries in the record, which form a small proportion of the whole, suffered from a clerical inaccuracy, and there was no alternative to their elimination from the survey.

A second difficulty is presented by the nature of the biological test applied at the time. Under the conditions then existing, rabbits were the only laboratory animals available, and those in numbers

only allowing the injection of each batch into two animals. The results with this species are not easy to interpret, especially as regards the occurrence of death towards the end of the week after injection. The dosage which had been adopted was 0·12 gramme per kilogramme, and for a long period it had been possible to stipulate that the two rabbits so injected should survive and remain healthy for a week. Shortly before the occurrence of the series of cases at Cherryhinton it had been found impossible to maintain this standard with full rigidity, if the supplies of drug needed by the army were to be available. Certain batches were passed, therefore, in which one rabbit died during the latter part of the week following injection. Later, owing to the poor condition of the war-time rabbits obtainable, the stipulation of a week's survival was temporarily abandoned, and attention was concentrated on precaution against immediate toxicity, by passing batches, the injection of which caused no toxic symptoms during the succeeding 48 hours. At one period the testing dose was temporarily lowered to 0·08 gramme per kilogramme, instead of 0·12 gramme per kilogramme. Only two such batches enter into the Cherryhinton record, and of these few injections were given. It is difficult, with the knowledge now available, to attach a precise significance to these apparent differences in the testing records of the different batches. An attempt, however, has been made to test the possibility of their connexion with the occurrence of jaundice in certain patients. The inquiry is rendered difficult by the fact that nearly every patient received, in the course of his treatment, injections from several batches. No batch can be identified as figuring exclusively, or predominantly, in the treatment of patients who suffered from toxic jaundice. The only comparison which it seemed possible to make has been carried out on the following lines.

The batches of arsenobenzol compounds used in the hospital during the period of the outbreak of jaundice have been classified, in accordance with their testing records, into

(1) Those which had passed the test in its full rigidity.

(2) Those which were allowed to pass although one of the two rabbits injected died before the end of the week of observation. There is no real evidence of inferiority of these batches to those in Class 1.

(3) Those which were allowed to pass on survival of the test animals for 48 hours without symptoms, or on a reduced dose, without shortening the observation period (2 only).

The use of the different batches was so unequal, some being used for many hundreds of doses, others for a few only, that the only satisfactory basis of comparison seems to be given by reckoning the numbers of doses of each of the three classes of preparations figuring in the treatment of the patients who died from jaundice and in that of the rest of the patients in the hospital. The following are the figures :

			Doses used in treatment of fatal cases.	Doses used in treatment of the whole population of the hospital during the same period.
Class 1.	.	.	26 = 21·8 %	1311 = 15·9 %
Class 2.	.	.	44 = 37·0 %	3320 = 40·2 %
	.	.	49 = 41·2 %	3621 = 43·9 %

If the distinction between the different classes has any real signifi-
cance, the result would seem to indicate that a rather smaller pro-
portion of the more toxic preparations was used in the treatment
of the sufferers from fatal jaundice than in that of the general popu-
lation of syphilitic patients treated in the hospital during the same
period.

There is no evidence, therefore, which would enable the Committee
to identify some specially toxic batch or batches of arsenobenzol
compounds as directly concerned in the causation of the outbreak.
At the same time, its occurrence during a period when the demand
for the drug temporarily outran the supply of material which would
satisfy the full rigidity of the test previously applied, may possibly
have some significance.

(d) SUMMARY.

Portobello Outbreak.

Little more need be said with regard to the group of cases occurring
at the Portobello Barracks, Dublin. The whole history indicates
that this was an isolated and unusual outbreak which only comes
within the scope of this report because the patients affected were
under treatment for syphilis with arsenobenzol preparations. There
can be no doubt that the fatalities were due to malignant malaria.
The Committee have no grounds for dissenting from the conclusion
come to by the Army Committee which studied the facts at the time,
viz. that the malarial infection was transmitted from one or more
malarial carriers to other patients by means of the apparatus used
for the injection of salvarsan solution. The arrangements obviously
did not preclude the possibility of regurgitation of blood into the
apparatus and the transference of such blood to other patients.
The Committee feel, however, that the available information renders
it somewhat difficult to understand how a sufficiently large amount
of blood to cause infection could have been conveyed to so many
patients, unless it so happened that each sufferer received, on one
occasion or another, his dose of salvarsan immediately after the
malaria carrier. This difficulty would be lessened if two malaria
carriers were concerned, a possibility suggested by a study of the
table giving the dates of injections, or if it may be accepted that
under some circumstances an extremely small quantity of blood
may suffice to cause infection.

The moral of the occurrence is clear as to the need for the greatest
precautions in the use of apparatus for injection of salvarsan to
a series of cases. The modern tendency to give the neo-preparations,
which are administered by syringe, naturally reduces the risk of any
similar accidents.

Cherryhinton Outbreak.

The Committee have devoted much time and attention to the
group of cases occurring at the Cherryhinton Military Hospital,
Cambridge. This outbreak is obviously similar in character to some
of those recorded in foreign literature and to the smaller groups of
cases of jaundice and acute atrophy of the liver in this country which
are referred to in this report. But when the particulars came first

before the Committee, the Cherryhinton group presented features which made it stand out from amongst the hitherto recorded instances of ill effects of arsenobenzol compounds. For example, it showed the occurrence within a comparatively short period of time of a rather large group of cases of jaundice, with a high percentage of fatal results, in a hospital which had previously been free from such complications, and at a time when other military hospitals in England presented no similar large incidence of liver disorders. It seemed desirable that a close investigation should be made with a view to ascertain, if possible, the explanation of the special characteristics of the outbreak. The Committee have made an exhaustive study of the available facts in the history of the outbreak and of the individual cases, and with a view to elucidate the causation they set on foot certain investigations. In this connexion they have to thank Professors Turnbull and Gunn, Drs. A. F. Wright, Candler, and Ainley Walker, for valuable services they have rendered.

As mentioned in their previous report, the Committee early in their inquiry came to the conclusion that the ill effects in this group of cases could not be dissociated from the administration of arsenobenzol preparations, although there were grounds for considering that some other factor might also be concerned. It seems advisable, however, to discuss various possible hypotheses as to the causation.

1. The idea that the outbreak had no connexion with the antisyphilitic treatment, but was merely due to the fortuitous occurrence of a group of cases affected by jaundice and liver atrophy as a consequence of the syphilis from which the patients suffered, may be mentioned merely to be dismissed. Acute atrophy of the liver due to syphilis alone has been so rare in the past that it is incredible that the whole group of cases could thus be accounted for, particularly as it is recognized that, since the introduction of salvarsan, the incidence of acute yellow atrophy of the liver has largely increased.

2. The hypothesis that the outbreak might have been due mainly to some infective factor, possibly supplemented by the effect of antisyphilitic treatment, is supported to some extent by (a) the explosive character and curve of the outbreak (see Chart II), (b) the hutment incidence (see Plan). By far the larger proportion of the cases, and all the deaths, occurred in patients living in huts in lines A and B ; lines C, D, and E were only lightly affected. This theory of an intercurrent infection, not necessarily of itself capable of producing jaundice but increasing the liability to toxic effects of persons under arsenobenzol treatment, is attractive, but no solid facts beyond (a) and (b) above can be adduced in its support.

Against the purely infective theory is the fact that jaundice was not observed in the gonorrhoea lines, except in one patient in line E, who was also under treatment for syphilis. On the other hand, the occurrence locally of mild jaundice amongst civilians might be held to be a point in its favour. On such a theory it might be assumed that an infective organism was introduced into A and B lines by the first patient (No. 13), or by some other patient who never developed noticeable symptoms of jaundice, and that its spread occurred by association of patients in the huts in A and B lines or through infection of the latrines. In this connexion the propinquity

of the latrines to Huts A 4 and A 7, in each of which 5 cases occurred, may be noted (see Plan).

On account of the well-known phenomena observed in association with the spread of certain infective disorders inquiries were made as to the earth temperatures and rainfall in Cambridge during the summer and autumn of 1917, but there was nothing to indicate that the changes recorded would help to account for this particular outbreak.

The possibility that the outbreak was one of spirochaetosis icterohaemorrhagica was considered, but since the clinical features did not correspond with the classical symptoms of infective jaundice, and there was no satisfactory evidence of the presence of the specific organism, the Committee feel that this may clearly be excluded.

3. The supposition that the outbreak might be due to some particular preparation or to some specially toxic batch of salvarsan naturally received consideration. There is no evidence to support this. Although one preparation was used more frequently than others, it was not employed exclusively even for the fatal cases. Various batches of this and other preparations were used both at Cherryhinton and at other hospitals without ill effects. The question as to specially toxic batches has already been discussed on p. 69. As stated there, although owing to the exigencies of the moment, the stringency of the animal tests for the toxicity of salvarsan which could be adopted fell below what is desirable, it seemed impossible to accept the view that the outbreak could be explained by the use of exceptionally toxic batches. On the other hand, it is conceivable that variations of toxicity might be one of several factors which may have contributed in some of the cases.

4. Whatever other factors may be concerned, the Committee feel that it is impossible to avoid the conclusion that a large share of responsibility must fall on the employment of arsenobenzol preparations, although it seems probable that the ill effects are only produced in persons either naturally susceptible or exposed also to the influence of other factors which aid the effect of the arsenical drugs.

With regard to the action of arsenobenzol compounds in aiding the production of jaundice and acute liver atrophy, the following points arise for consideration, viz. size of individual doses, total dosage, spacing of doses, and variations in methods of administration. So far as the size of individual doses and variations in methods of administration are concerned, the information at the disposal of the Committee indicates that no change had occurred in the procedure adopted prior to the outbreak, and that the ' epidemic ' came spontaneously to an end without any change in method. As regards total dosage it may be observed that, on the whole, the total amount of arsenobenzol given at Cherryhinton in the fatal cases was in excess of that given to the non-fatal cases. Of the 15 fatal cases 7 had each received a total of 4 grammes administered in 10 injections over a period varying from 77–84 days. Further it is to be noted that 3 of these 7 fatal cases which had received a total of 4 grammes, and one fatal case which had received 2·5 grammes at Cherryhinton had also received arsenobenzol treatment elsewhere before admission to Cherryhinton. Of the remaining fatal cases

5 received each a total of 2·8 grammes in seven injections over a period of 42–44 days, and one case 3·5 grammes. The lowest total amount of arsenobenzol injected in fatal cases was 2·2 grammes in 5 injections over a period of 24 days. (November 6, 0·3 ; 9, 0·4 ; 16, 0·5 ; 23, 0·5 ; 30, 0·5 Kharsivan). The individual doses injected varied as a rule between 0·3 to 0·5 grammes. Of the 22 non-fatal cases only 2 received as much as 4 grammes. Others received varying amounts from 3·1 to 0·9 grammes, the latter being the lowest total amount injected over the period of treatment.

Only two of the non-fatal cases had received previous treatment with arsenobenzol preparations. These considerations would appear to indicate that high dosage of arsenobenzol preparations may have had some influence in encouraging the advent of jaundice and in increasing the risk of fatal result. On the other hand a similar total dosage had been given to many patients without obvious ill effects.

As regards the spacing of doses, in some of the fatal cases as mentioned above, the interval between the first and second dose was as short as 3–4 days. But at the time of the outbreak a similar shortening of the interval between the first and second doses was common in other Military Hospitals in which jaundice and liver atrophy were not observed. On the other hand a close scrutiny indicates that, contrary to usual practice, the ordinary course of 2·8 grammes was compressed at this hospital during the period in question into 42 days instead of 50 days. This undue pushing of the drug, adopted no doubt in order to restore soldiers as early as possible to efficiency for military service, may undoubtedly have tended to increase the liability to jaundice and liver atrophy. But it will be observed that some of the fatal cases received as little as 2·2 to 2·8 grammes total dose of arsenobenzol and some of the non-fatal cases which nevertheless suffered from jaundice had as little as 0·9 grammes. Further, other patients in the hospital at the time, whose records were not before the Committee and who did not suffer either from jaundice or acute atrophy of the liver were treated on similar lines, many receiving as high a dosage compressed into an equally short period of time without ill results. Again, the question of dosage does not explain the extraordinary incidence of ill effects in patients in lines A and B as compared with lines C and D.

The Committee consider that the outbreak of jaundice and fatal atrophy of the liver in the Cherryhinton cases must be attributed largely to the employment of arsenobenzol compounds, and that the total dosage and the compression of the usual course into a shorter period of time contributed to the ill results, but that these factors alone do not fully account for the outbreak.

What further factor or factors [1] were concerned the Committee are unable to decide, and it may be noted that inquiries as to the causation of similar outbreaks elsewhere have proved equally fruitless.

Excluding the Portobello outbreak which was of quite an exceptional nature, and considering only the series of cases at Cherryhinton,

[1] In this connexion reference may be made to the statement by Hayashi and Kibata (1922) that they have discovered, in the liver and other organs of a case which they regarded as typical acute yellow atrophy, a new spirochaete which is neither the leptospira of infective jaundice nor the spironeme of syphilis.

it will be seen that the conclusions reached are in harmony with those arrived at from a more general survey of the evidence based chiefly on the published literature of the subject.

TABLE X.   *Jaundice Cases—Cherryhinton Hospital.*

No.	Initials.	Age.	Hut.	Admission.	Last dose of 606 or 914.	Onset of Symptoms.	Death.	Remarks.
1	J. W.	22	A.4	9. 5.17	3. 7.17	16. 7.17	18. 7.17	
2	H. W.	27	B.2	17. 7.17	19.10.17	15. 8.17	..	Jaundiced but not ill. 606 stopped for 6 weeks, then 914 given.
3	W. W.	17	A.4	15. 6.17	14. 8.17	4. 9.17	..	
4	R. J. N.	20	A.2	21. 8.17	26.10.17	8. 9.17	..	Treatment stopped for 14 days then 914 given.
5	L. B.	26	B.5	20. 8.17	7. 9.17	3.11.17	..	Eight injections 606 in 1915 and nine (3·5 gm.) earlier in 1917.
6	A. J. G.	39	A.7	9. 7.17	11. 9.17	23. 9.17	..	
7	F. D.	25	A.6	18. 9.17	16.10.17	4.10.17	..	Jaundiced but not really ill.
8	G. W.	24	C.5	29. 9.17	13.10.17	13.10.17	..	
9	D. D.	36	A.7	2. 8.17	18. 9.17	13.10.17	14.10.17	
10	S.	34	A.6	9. 7.17	2.10.17	18.10.17	19.10.17	
11	W. L.	34	A.7	29. 6.17	28. 9.17	23.10.17	24.10.17	
12	W. N.	41	C.9	13. 9.17	27.10.17	30.10.17	..	Relapsing attacks of Jaundice previously.
13	G. J. W.	31	B.8	6. 2.17	4. 4.17	9. 4.17	..	First case of series.
14	W. H.	33	A.8	3. 9.17	9.11.17	12.11.17	17.11.17	Had some 606 previously.
15	A. G. W.	29	A.7	8. 9.17	23.11.17	30.11.17	2.12.17	
16	W.	40	B.7	2.10.17	16.11.17	19.11.17	..	
17	J. C. B.	41	B.3	30.10.17	23.11.17	2.12.17	..	Received two injections of Galyl in January 1918.
18	J. L.	21	A.4	11. 9.17	4.12.17	6.12.17	..	
19	H. O'H.	19	A.4	5. 9.17	23.10.17	27.11.17	28.11.17	
20	H. P.	24	E.8	2.11.17	9. 1.18	8.12.17	..	Spirochaete found in blood.
21	L. P.	30	A.8	30.11.17	29. 1.18	22.12.17	..	
22	B. W. P.	29	B.3	4. 9.17	23.11.17	6. 1.18	14. 1.18	Had 606 previously. Malaria in India.
23	F. H.	19	A.4	20.10.17	4. 1.18	7. 1.18	..	
24	J. S.	21	B.6	21. 8.17	9.11.17	20.12.17	20. 1.18	
25	E. H.	?27	B.6	8.10.17	23.11.17	7. 1.18	18. 1.18	
26	G. H. D.	19	A.7	2.11.17	30.11.17	31.12.17	4. 1.18	Had 606 previously.
27	J. S.	32	A.5	4. 7.17	25. 9.17	22.10.17	24.10.17	
28	S. P.	33	A.9	25. 6.17	21. 9.17	11.17	..	
29	I. C.	23	C.6	31. 1.18	16. 2.18	23. 2.18	..	Jaundiced but not really ill.
30	R. H. McD.	34	B.2	30. 6.17	2.10.17	End of Nov. '17	3.12.17	Had 606 previously.
31	J. A. C.	33	B.2	26.10.17	11.12.17	24. 1.18	..	
32	E. W.	24	B.8	15. 9.17	20.10.17	?12. 1.18	..	
33	C. W.	20	Det	1. 3.18	16. 3.18	22. 3.18	..	
34	J. V. D.	29	C.7	22. 1.18	6. 3.18	23. 3.18	..	Two injections of 606 previously.
35	J. P.	32	D.6	14. 3.18	3. 4.18	6. 4.18	..	
36	J. E. C.	23	A.2	10.11.17	29. 1.18	15. 3.18	26. 3.18	Had 606 previously.
37	D. C.	29	B.7	17. 7.17	31. 8.17	26.10.17	2.11.17	

TABLE XI. *Cherryhinton Cases. Particulars as to administration of Salvarsan preparations.*

(Kh.=Kharsivan, A.B.=Arsenobillon, N.A.B.=Novarsenobillon.)
(Arranged in order of date of admission to Cherryhinton.)

No.	Initials.	Date of admission.	Salvarsan preparations used, and batch numbers.	Total amount in gm.	Date of				Interval in days between last dose and onset of symptoms	Date of death.
					First Dose.	Intermediate doses.	Last dose.	Onset of symptoms.		
		1917			1917					
13	G. J. W.	Feb. 6	Kh. 307, 287, 315, 373, 348	2·6	Feb. 17	Feb. 21, 28; Mar. 14, 21, 28	Apr. 4	Apr. 9	5	..
1	J. W.	May 9	Kh. 404, 388, 362, 463, 468	2·8	May 22	May 25; June 1, 12, 19, 26	July 3	July 16	13	18. 7.17
3	W. W.	June 15	Kh. 560, 404, 527, 524	2·8	June 29	July 6, 13, 24, 31; Aug. 7	Aug. 14	Sept. 4	21	..
28	S. P.	June 25	Kh. 404, 523, 524, 527, 560, 573	4·0	July 3	July 6, 13, 24, 31; Aug. 7, 14; Sept. 11, 14	Sept. 21	Nov. ?	+40	..
11	W. L.	June 29	Kh. 560, 523, 524, 527, 573	4·0	July 6	July 10, 17, 27; Aug. 3, 10, 17; Sept. 14, 21	Sept. 28	Oct. 23	25	24.10.17
30	R H. Mc.D.	June 30	Kh. 404, 524, 527, 573; A.B. 836	4·0	July 3	July 6, 13, 24, 31; Aug. 7, 14; Sept. 18, 25	Oct. 2	After Nov. 24	Over 50	3.12.17
27	J. S.	July 4	Kh. 523, 524, 527, 560, 573; A.B. 707	4·0	July 6	July 10, 13, 27; Aug. 3, 10, 17; Sept. 11, 18	Sept. 25	Oct. 22	27	24.10.17
6	A. J. G.	July 9	Kh. 560, 388, 524, 527, 528; A.B. 707	3·1	July 13	July 17, 24; Aug. 3, 10, 17, 24	Sept. 11	Sept. 23	12	..
10	S.	July 9	Kh. 560, 388, 524, 527, 528, 573; A.B. 707	4·0	July 13	July 17, 24; Aug. 3, 10, 17, 24; Sept. 18, 25	Oct. 2	Oct. 18	16	19.10.17

No.	Initials	Date	Treatment	Dose	Date	Injections	Date	Date	Days	Remarks
2	H.W.	July 17	Kh. 388, 404, 524. 527; N.A.B. 118	2.8	July 24	July 28; Aug. 3, 14,* 21; Oct. 12	Oct. 19	Aug. 15	1†	..
37	D.C.	July 17	Kh. 388, 527, 528, 560	2.8	July 20	July 24, 31; Aug. 10, 17, 24	Aug. 31	Oct. 26	56	2.11.17
9	D.D.	Aug. 2	Kh. 527, 560; A.B. 707	2.8	Aug. 7	Aug. 10, 17, 28; Sept. 4, 11	Sept. 18	Oct. 13	25	14.10.17
5	L.B.	Aug. 20	Kh. 528, 560 ‡	1.2	Aug. 24	Aug. 31	Sept. 7	Nov. 3	57	..
4	R.J.N.	Aug. 21	Kh. 528, 560; N.A.B. 118	2.75	Aug. 24	Aug. 28; Sept. 7,* 28, Oct. 5, 12, 19 Nov. 2	Oct. 26	Sept. 8	1†	..
24	J.S.	Aug. 21	Kh. 528, 560, 573, 581, 585	4.0	Aug. 24	Aug. 28; Sept. 4, 14, 21, 28; Oct. 5, 26; Nov. 2	Nov. 9	Dec. 20	41	20. 1.18
14	W.H.	Sept. 3	Kh. 560, 573, 585; A.B. 707, 231, 251	2.5	Sept. 7	Sept. 18, 25; Oct. 2, 9; Nov. 2	Nov. 9	Nov. 12	3	17.11.17
22	B.W.P.	Sept. 4	Kh. 560, 573, 581, 585; A.B. 836	4.0	Sept. 7	Sept. 11, 18, 28; Oct. 5, 12, 19; Nov. 9, 16	Nov. 23	Jan. 6, 1918	44	14. 1.18
19	H.O'H.	Sept. 5	Kh. 560, 573; A.B. 245	2.8	Sept. 11	Sept. 14, 21; Oct. 2, 9, 16	Oct. 23	Nov. 27,1917	35	28.11.17
15	A.G.W.	Sept. 8	Kh. 560, 573, 585; A.B. 245	3.5	Sept. 11	Sept. 14, 21; Oct. 2, 9, 16, 23; Nov. 16	Nov. 23	Nov. 30	7	2.12.17
18	J.L.	Sept. 11	Kh. 560, 573; A.B. 707, 245, 246, 118	4.0	Sept. 14	Sept. 15 ((?) 18), 23; Oct. 5, 12, 19, 26; Nov. 20, 27	Dec. 4	Dec. 6	2	..
12	W.N.	Sept. 13	A.B. 231, 251, 245, 260	2.8	Sept. 15	Sept. 19, 26; Oct. 6, 13, 20	Oct. 27	Oct. 30	3	Relapsing jaundice previously. First injection at Hastings.
32	E.W.	Sept. 15	A.B. 231, 251, 245	2.8	Sept. 9	Sept. 22, 29; Oct. 6, 13	Oct. 20	?Jan. 12, 1918	?84	..
7	F.D.	Sept. 18	A.B. 836, 231, 251, 245	1.3	Sept. 21	Sept. 25; Oct. 2 *	Oct. 16	Oct. 4, 1917	2†	..
8	G.W.	Sept. 29	A. B. 245, 251	0.9	Oct. 3	Oct. 6	Oct. 13	Oct. 13	same day	..
16	W.	Oct. 2	A.B. 251, 245, 260; Kh. 581, 585	2.8	Oct. 5	Oct. 9, 16, 26: Nov. 2, 9	Nov. 16	Nov. 19	3	..

* Jaundice appeared after this injection.
† See above note.
‡ This man was treated with 3·5 gm. Kharsivan in Cherryhinton Hospital from Feb. to May 1917.

TABLE XI (continued).

(Kh.=Kharsivan, A.B.=Arsenobillon, N.A.B.=Novarsenobillon.)
(Arranged in order of date of admission to Cherryhinton.)

No.	Initials.	Date of admission.	Salvarsan preparations used, and batch numbers.	Total amount in gm.	Date of				Interval in days between last dose and onset of symptoms	Date of death.
					First Dose.	Intermediate doses.	Last dose.	Onset of symptoms.		
25	E. H.	1917 Oct. 8	A.B. 251, 245 ; Kh. 585	2·8	1917 Oct. 12	Oct. 16, 23 ; Nov. 2, 9, 16	1917 Nov. 23	1918 Jan. 7	45	18. 1.18
23	F. H.	Oct. 20	Galyl. 353, 378, 373, 573, 380, 394 ; N.A.B. 223, 225	3·2	Oct. 30	Nov. 6, 13, 20, 27 ; Dec. 4, 28	1918 Jan. 4	Jan. 7	3	..
31	J. A. C.	Oct. 26	Kh. 581, 585, 116	2·8	Oct. 30	Nov. 2, 9, 20, 27 ; Dec. 4	1917 Dec. 11	Jan. 24	44	..
17	J. C. B.	Oct. 30	Kh. 585 ; Galyl. 405, 410	1·5	Nov. 13	Nov. 16, 23 ; * Jan. 8	1918 Jan. 15	1917 Dec. 2	9†	..
20	H. P.	Nov. 2	Kh. 585 ; N.A.B. 223, 225	2·8	Nov. 9	Nov. 13, 20, 30 ; Dec 7,* 28	Jan. 9	Dec. 8	1†	..
26	G. H. D.	Nov. 2	Kh. 585	2·2	Nov. 6	Nov. 9, 16, 23	1917 Nov. 30	Dec. 31	31	4. 1 18
36	J. E. C.	Nov. 10	Kh. 585, 116, 619 ; N.A.B. 77	4·7	Nov. 13	Nov. 16, 23 ; Dec. 4, 11, 18, 24 ; Jan. 15, 22	1918 Jan. 29	Mar. 15	45	26 3 18
21	L. P.	Nov. 30	Kh. 585, 116, 619, 721	1·4	Dec. 7	Dec. 11, 18 *	Jan. 29	1917 Dec. 22	4†	.
34	J. V. D.	1918 Jan. 22	A.B. 272, 87 ; Kh. 721	2·8	1918 Jan. 23	Jan. 26 ; Feb. 2, 13, 20, 27	Mar. 6	1918 Mar. 23	17	..
29	L. C.	Jan. 31	A.B. 57	0·9	Feb. 6	Feb. 9	Feb. 16	Feb. 23	7	..
33	C. W.	Mar. 1	Kh. 721, 735, 757	0·9	Mar. 6	Mar. 9	Mar. 16	Mar. 22	6	..
35	J. P.	Mar. 14	Kh. 757	0·9	Apr. 6	Mar. 27	Apr. 3	Apr. 6	3	

* Jaundice appeared after this injection.
† See above note.

TABLE XII A. *Cherryhinton Fatal Cases.*

Hut.	File number.	Age.	Stage of disease on commencing treatment.			Other disease	Amount of Arseno-benzol in grammes.	Total number of injections.	Period of treatment in days.	Amount of Mercury in grains.	Potassium Iodide administered or not.	Interval in days between last injection and onset of symptoms.	Interval in days between the onset of symptoms and death.
			Primary negative Wassermann.	Early generalized with positive Wassermann.	Tertiary and late cases generally.								
A. 4	(1)	22	..	Yes	..	Gono.	2·8	7	42	8 gr	Yes	13	2
A. 7	(9)	36	..	..	Yes	Gono	2·8	7	42	8 ,,	No	25	1
A. 6	(10)	34	..	..	Yes	..	4·0	10	81	11 ,,	Yes	16	1
A. 7	(11)	34	..	Yes	..	Gono.	4·0	10	84	11 ,,	Yes	25	—
A. 8	(14)	33	..	..	Yes	..	2·5 *	7	65	9 ,,	Yes	3	5
A. 7	(15)	29	..	..	Yes	..	3·5	9	73	10 ,,	Yes	7	2
A. 4	(19)	19	Yes	..	..	..	2·8	7	42	8 ,,	No	35	1
B. 3	(22)	29	..	Yes	..	..	4·0 †	10	77	8 ,,	Yes	44	8
B. 6	(24)	21	..	Yes	..	..	4·0	10	77	11 ,,	Yes	41	31
B. 6	(25)	?27	Indurated sore	..	..	..	2·8	7	42	8 ,,	No	45	11
A. 7	(26)	19	..	Yes	..	..	2·2	5	24	8 ,,	Yes	31	4
A. 5	(27)	32	..	Yes	..	..	4·0	10	81	11 ,,	Yes	27	2
B. 2	(30)	34	..	Yes	..	..	4·0 ‡	10	81	11 ,,	Yes	over 50	about 8
A. 2	(36)	23	..	Yes	..	..	4·7 §	10	77	11 ,,	Yes	45	11
B. 7	(37)	29	..	Yes	..	Gono.	2·8	7	44	8 ,,	No	56	7

* Had received two previous injections of arsenobenzol compounds and mercury at Brighton but date not given.
† Five months previously had full course at Hilsea.
‡ Three weeks previously had completed a course (of 2·8 gm.) at Chiseldon.
§ Thirteen months previously had been treated with 2·8 gm. '606' at Etchinghill.

TABLE XII B. *Cherryhinton Non-Fatal Cases.*

Hut.	File number.	Age.	Stage of disease on commencing treatment.			Other diseases.	Amount of Arseno-benzol used before onset of symptoms.	Total number of injections.	Period of treatment in days.	Amount of Mercury in grains.	Potassium Iodide administered or not.	Interval in days between last injection and onset of symptoms.
			Primary negative Wassermann.	Early generalized with positive Wassermann.	Tertiary and late cases generally.							
B. 2	(2)	27	Yes	..	..	..	1·3	4	21	6	No	1
A. 4	(3)	17	Yes	..	..	Scabies	2·8	7	46	8	Yes	21
A. 2	(4)	20	..	Yes	..	..	0·9	3	14	2	No	1
B. 5	(5)	26	..	..	Yes	Gono. and Arthritis	1·2*	3	14	3	No	57
A. 7	(6)	39	..	..	Yes	'War shock'	3·1	8	60	10	No	12
A. 6	(7)	25	..	Yes	..	..	0·9	3	11	?	..	2
C. 5	(8)	24	..	Yes	..	Had suffered repeatedly from Jaundice	0·9	3	10	3	No	Same day
C. 9	(12)	41	Yes	..	..		2·8	7	42	8	No	3
B. 8	(13)	31	..	Yes	..	..	2·6	7	46	?	Yes	5
B. 7	(16)	40	..	Yes	..	..	2·8	7	42	8	No	3
B. 3	(17)	41	..	Yes	..	..	0·9	3	10	2	No	9
A. 4	(18)	21	..	Yes	..	Gono.	4·0	10	81	11	No	2
E. 8	(20)	24	..	Yes	..	Gono.	1·8	5	28	5	No	1
A. 8	(21)	30	..	..	Yes	..	0·9	3	11	4	No	4
A. 4	(23)	19	..	Yes	..	..	3·2	8	66	10	Yes	3
A. 9	(28)	33	..	Yes	..	..	4·0	10	80	11	No	40
C. 6	(29)	23	..	Yes	..	..	0·9	3	14	3	No	7
B. 2	(31)	33	..	Yes	..	..	2·8	7	44	8	No	44
B. 8	(32)	24	..	Yes	..	..	2·5	6	41	7	No	84
Det.	(33)	20	..	Yes	..	..	0·9	3	10	3	No	6
C. 7	(34)	29	..	Yes	..	..	2·8	7	42	8	Yes	17
D. 6	(35)	32	..	Yes	..	Gono.	0·9	3	11	3	No	3

* A relapse case from 1911. Is said to have had 2·4 gm. at Havre in 1915, and 3·5 gm. at Cherryhinton Feb. to May 1917.

TABLE XIII. *Cherryhinton Military Hospital Jaundice Cases. Hut by Hut Analysis, to accompany plan.* (*Page* 65.)

Hut No.	Case No.	Admitted on.	Discharged on.	Symptoms began.		Date Died.
A.2	4	2. 8.17	3.11.17	8. 9.17	S.[1]	..
,,	36	10.11.17	4. 2.18	15. 3.18	S.	26. 3.18
A.4	1	9. 5.17	17. 7.17	16. 7.17	S.	18 7.17
,,	3	15. 6.17	7. 9.17	4. 9.17	V.M.[2]	..
,,	18	11. 9.17	6.12.17	6.12.17	M.[3]	..
,,	19	5. 9.17	7.11.17	27.11.17	S.	28.11.17
,,	23	20.10.17	7. 1.18	7. 1.18	V.M.	..
A.5	27	4. 7.17	1 10.17	22.10.17	S.	24.10.17
A.6	7	18. 9.17	24.10.17	4.10.17	V.M.	..
,,	10	9. 7.17	8.10.17	18.10.17	S.	19.10.17
A.7	6	9. 7.17	5.10.17	23. 9.17	V.M.	..
,,	9	2. 8.17	13.10.17	13.10.17	S.	14.10.17
,,	11	29. 6.17	23.10.17	23.10.17	S.	24.10.17
,,	15	8. 9.17	30.11.17	30.11.17	S.	2.12.17
,,	26	2.11.17	29.12.17	31.12.17	S.	4. 1.18
A.8	14	3. 9.17	15.11.17	12.11.17	S.	17.11.17
,,	21	30.11.17	31.12.17	22.12.17	V.M.	..
A.9	28	25. 6.17	30.10.17	11.17	M.	..
B.2	2	17. 7.17	22.10.17	15. 8.17	V.M.	..
,,	30	30. 6.17	8.10.17	end 11.17	S.	3.12.17
,,	31	26.10.17	18.12.17	24. 1.18	S.	..
B.3	17	30.10.17	2.12.17	2.12.17	M.	..
,,	22	4. 9.17	1.12.17	6. 1.18	S.	14. 1.18
B.5	5	20. 8.17	10.11.17	3.11.17	V.M.	..
B.6	24	21. 8.17	15.11.17	20.12.17	S.	20. 1.18
,,	25	8.10.17	1.12.17	7. 1.18	S.	18. 1.18
B.7	16	2.10.17	19.11.17	19.11.17	M.	..
,,	37	17. 7.17	17. 9.17	26.10.17	S.	2.11.17
B.8	13	6. 2.17	23. 4.17	9. 4.17	M.	..
,,	32	15. 9.17	31.10.17	1.18	S.	..
C.5	8	29. 9.17	27.10.17	13.10.17	M.	..
C.6	29	31. 1.18	24. 2.18	23. 2.18	V.M.	..
C.7	34	22. 1.18	23. 3.18	23. 3.18	M.	..
C.9	12	13. 9.17	30.10.17	30.10.17	M.	..
D.6	35	14. 3.18	7. 4.18	6.. 4.18	V.M.	..
E.8	20	2.11.17	14. 1.18	8.12.17	S.	..
Detention	33	1. 3.18	25. 3.18	22. 3.18	M.	..

NOTE.—All fatal cases of jaundice occurred in A and B lines.

[1] Severe= S.   [2] Very Mild= V.M.   [3] Moderate= M.

VIII. SUMMARY AND CONCLUSIONS

(a) GENERAL SUMMARY

1. No special arsenobenzol preparation can be regarded as more likely than others to produce ill effects.

2. Large series of cases of syphilis have been treated without the occurrence of any serious ill effect, although a small percentage of slighter reactions, chiefly vasomotor and mild skin reactions, is to be expected in every large collection of patients treated with arsenobenzol compounds.

3. Errors in technique cannot account for more than a few serious accidents; fatalities have occurred even under the most careful control in large and completely equipped hospitals.

4. The most important ill effects which may end fatally are :
   (a) Encephalitis haemorrhagica.
   (b) Acute yellow atrophy of the liver.
   (c) Exfoliative dermatitis and its complications.

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5. In European literature, and especially in the very large German literature, encephalitis haemorrhagica is most frequently described. In Great Britain and America, however, exfoliative dermatitis and its septic complications have accounted for most fatal accidents. Acute yellow atrophy of the liver is difficult to place in order of frequency, being distinguished from the other serious ill effects by its peculiar liability to occur in localized outbreaks. Single cases however, are by no means unknown.

6. Encephalitis haemorrhagica occurs within two to five days after an injection, and presents a very characteristic clinical picture. Its incidence is most frequent after the second injection, but it may ensue after any one of a series of injections. It must be considered as due to the arsenobenzol treatment.

7. Disorders of the liver following treatment by arsenobenzol compounds may for convenience be grouped into :

    (a) Early (benign) jaundice.

    (b) Late (severe) jaundice.

    (c) Acute yellow atrophy of the liver, commonly the sequel of late jaundice, and clinically and pathologically indistinguishable from the same condition occurring in the known absence of syphilis.

8. Skin reactions following arsenobenzol are fairly common, and usually slight and transient. The one reaction of serious significance is exfoliative dermatitis.

9. Vasomotor phenomena occur in a small proportion of cases even under the best conditions. Although alarming at the time they are rarely, if ever, fatal. They appear to bear no relation to anaphylaxis, and the use of this word in describing them is to be deprecated. Febrile disturbances, headache, diarrhoea, and vomiting also occur, but are usually of slight moment.

10. Certain other ill effects of arsenobenzol treatment, which may even end fatally, are met with only very rarely. These include acute renal damage, ulcerative enteritis, polyneuritis, and aplastic anaemia.

11. Certain lessons as regards dosage and frequency of administration have been learned from the experiences of the late war. During the war period, following a definite military policy, the dosage and frequency were in some places increased over what would nowadays be recommended. The Committee believe that both dermatitis and hepatic disorders may in part at least be due to excessive frequency and size of the dose.

(b) Conclusions.

In reviewing the ill effects which have been attributed to treatment with salvarsan, we may consider, in the first place, those of which the causal connexion with the treatment is perfectly clear. In the case of these it is of interest to inquire to what extent they correspond with the known results of acute or of chronic poisoning by arsenic given in inorganic form, and to what extent, on the other hand, they must be attributed to the administration of the arsenic in the form of this particular organic complex. In making such a comparison it is not justifiable to assume that such ill effects of

salvarsan, as do not exactly correspond to the known phenomena of poisoning by arsenic, are necessarily due to the action of the complex salvarsan molecule as a whole, and not at all to the arsenic which it contains. The method by which salvarsan is administered, its physical properties, special solubility relations, and the mode of its coming into action in the body, must all be taken into account. Acute poisoning by inorganic arsenic is familiar as the result of swallowing a single large dose, while chronic poisoning is seen as the cumulative effect of long continued administration of individually sub-toxic doses. In the case of salvarsan administration we are dealing with parenteral administration of a series of doses, each sufficient to produce symptoms of acute poisoning if the arsenic it contained were injected in inorganic form, but holding it in the form of an organic complex which is only slowly decomposed in the body, so that the liberation of arsenic continues for some time after the administration is finished.

If salvarsan as a poison, then, were to be regarded merely as a vehicle of arsenic, we should expect any bad effects which it pro-duced to correspond rather to the chronic type, in spite of the relatively short period occupied by its administration. Further, since it is injected parenterally and not given by the mouth, we should expect that such of its effects as correspond to those of arsenic would be rather the general systemic effects of arsenic as a capillary poison, than the predominantly gastro-intestinal effects seen in acute poisoning with inorganic arsenic administered by the mouth.

When these considerations are borne in mind, certain of the ill effects which are recognized as being due to salvarsan may without hesitation be ascribed to the arsenic which it contains. The occa-sional occurrence of gastritis and enteritis, for example, may be compared with the similar conditions which occasionally arise as the result of the introduction of inorganic arsenic into the system by parenteral routes, as when it is accidentally absorbed from a wound. With even more confidence can the effects on the skin, and especially the exfoliative dermatitis which we have seen to be one of the commonest of the serious ill effects of salvarsan treat-ment, be regarded as simply the result of poisoning by arsenic in specially susceptible patients. Poisoning of the capillary endo-thelium being the characteristic feature of acute poisoning by inorganic arsenic, it is possible that the condition known as ' encephalitis haemorrhagica ', being associated with excessive transudation and capillary haemorrhages, should also be classed as arsenical poisoning. Rarer effects of salvarsan, such as polyneuritis and damage to the renal epithelium, also correspond to well recog-nized effects of arsenic.

Of the ill effects which can, with certainty, be attributed to the administration of salvarsan, there remain those which sometimes follow immediately upon injection—the so-called ' crises nitri-töides ', ' shock-effect ', or ' vasomotor phenomena '. Since these also are characterized by symptoms of capillary poisoning, it might seem reasonable to attribute them to acute arsenical intoxication. It has been seen, however, that there is much evidence connecting

them rather with the physical properties of the drug—their association with rapidly precipitating solutions of old salvarsan, with imperfectly soluble specimens of neosalvarsan, and the record of their appearance in a violent and dangerous form in cases in which the old salvarsan has, through oversight, been injected intravenously in the acid state. (See p. 10 of first report of the Salvarsan Committee.) Such observations, and the usually rapid evanescence of the symptoms, seem to show clearly that we are here dealing with a phenomenon which has no direct connexion with the presence of arsenic in the molecule, but is the result of a disturbance of the colloidal condition of the blood. The now well-recognized association between the frequency and severity of such symptoms and the use of contaminated water, or other technical defects in the preparation of the material for injection, is also difficult to reconcile with the view that they are due to arsenical poisoning

So that, of the ill effects which can be definitely attributed to treatment with salvarsan, some can be regarded as due to arsenical poisoning, while others seem to be due rather to the peculiar physical properties and solubilities of the substances included in this group of remedies.

There remain for consideration the important effects on the liver ; the connexion of these with salvarsan has been somewhat obscured by the frequently long intervals elapsing between the end of the treatment and the appearance of symptoms of hepatic trouble, and also by the fact that similar troubles were observed as the result of syphilis in the pre-salvarsan era. This latter fact forbids the assumption that every case of severe jaundice or acute yellow atrophy of the liver arising during the treatment of syphilis by salvarsan is due to the treatment. On the other hand, there are weighty reasons against acquitting salvarsan of all share in the production of such cases.

These reasons are as follows : (1) There is an increasing body of evidence that the arsenobenzol preparations produce a deleterious effect upon the functional efficiency of the liver, and that some degree of hepatic insufficiency is demonstrable three months after a course of the drug, thus furnishing at all events a groundwork for hepatic complications. (2) Evidence tends to show that jaundice and acute yellow atrophy have increased in frequency since the introduction of salvarsan, especially amongst the young adult male population which furnishes the majority of recent syphilitics. (3) The relation in time between the occurrence of these accidents and the administration of a course of salvarsan is too frequent to be merely accidental. (4) There is evidence to show that the pushing of salvarsan treatment, with the object of effecting a speedy cure, has been associated with an increased liability to jaundice and acute yellow atrophy of the liver.

Further, while these effects on the liver cannot, like the dermatitis, for example, be brought into relation with known ill effects of inorganic arsenic, the organic portion of the salvarsan molecule has a sufficiently close relation to known organic liver poisons, such as toluylendiamine, to render plausible the supposition that the effects may be due to the action of the salvarsan molecule itself, or

of some early derivative formed from it in the body, acting on an exceptionally sensitive individual.

The chief difficulties in the way of the conclusion that the majority, at any rate, of the serious liver troubles following salvarsan treatment are due solely to a poisonous action of the drug, have been presented by the frequently grouped incidence of the cases, and the paucity of evidence of comparable effects produced by the experimental administration of salvarsan to animals. Exactly the same difficulties were found in attributing to simple poisoning by trinitrotoluene the cases of liver atrophy which occurred during the war among workers industrially exposed to that substance. The second objection, based on the failure of salvarsan to produce any pronounced effects on the livers of experimental animals, even when given in proportionally enormous doses, has recently been greatly weakened by the observation of Hooper, Kolls, and Wright, that in the dog an extensive necrosis of the centres of the liver lobules is, in fact, a frequent result of the injection of salvarsan.

The tendency of the cases of severe jaundice and liver atrophy in man to occur in the form of small outbreaks, localized to one or another hospital and restricted in time to a few months of its practice, has not yet received an adequate explanation. The Committee have not found any evidence to support the suggestion that it is to be attributed to the use of specially toxic batches of the drug or to faulty methods of administration. There is, on the other hand, some evidence that unwise pushing of the dosage, both as regards size and frequency, may be a factor of some importance in causing an outbreak. This cannot, however, by itself be regarded as a sufficient explanation of the tendency of severe liver affections following salvarsan, to occur in groups like small epidemic outbreaks, and we cannot lightly dismiss the suggestion of a further local factor, acting with increased force upon a liver already damaged by salvarsan. As in the case of the similarly puzzling outbreaks of liver atrophy among workers in trinitrotoluene, the suggestion of an adventitious infection has been made. The most definite suggestion of this kind was made by Stuart McDonald, but the Committee do not feel able to attach much importance to his post-mortem finding of a coliform bacillus in the affected livers—since post-mortem evidence of infection by such bacilli is notoriously misleading. Only blood-cultures during life could afford the necessary proof, and evidence of this kind is entirely wanting. There is, however, one fact which may be of significance, namely, the association of ' salvarsan jaundice ' with concurrent epidemics of catarrhal jaundice amongst the surrounding population : this association has been noted on several occasions—e. g. the Cherryhinton outbreak, the outbreak reported by Todd amongst the Rhine forces, and the observations of Stokes and Ruedemann in America. The cause of catarrhal jaundice is not certainly known, but its tendency to epidemic prevalence is suggestive of infection.

As an argument against the infective character of liver atrophy after salvarsan is to be noted the opinion of Professor Turnbull, whose careful histological observations lead him to regard it as a toxic rather than as an infective process.

A further parallel between these occasional later sequelae of salvarsan treatment and those associated with the absorption of trinitrotoluene is provided by the cases of aplastic anaemia, which have been observed as rare occurrences in both cases. The points of similarity are indeed so many—the occasional occurrence of severe jaundice and liver atrophy, often appearing months after treatment or exposure has ceased ; the tendency of the cases to appear in localized outbreaks, naturally giving rise to the suggestion of an associated infective cause ; and the occurrence of much rarer cases of aplastic anaemia—that it is difficult to avoid the suggestion that we are dealing with processes of a fundamentally similar nature. This view is strengthened by the consideration that salvarsan is an amino-benzene derivative, and that there is reason to associate the poisonous action of trinitrotoluene with a reduction of its nitro-groups to amino-groups in the body.

Upon the evidence before them, therefore, the Committee think it probable that many of the ill effects of salvarsan may be attributed directly to its arsenical content ; that others are due rather to its peculiar solubilities and the physical properties of its solutions ; and that others again, in particular the effects on the liver, and possibly those on the bone marrow, are due to the chemical nature of the whole compound, as an amino-phenol derivative, with the possibility that this type of poisonous action is dependent for its occurrence on the presence of adjuvant circumstances, of a nature as yet unknown.

There is a consensus of opinion amongst those concerned with the treatment of venereal disease that the arsenobenzol preparations are more efficacious than any other drugs yet available for the cure of syphilis. Although it is true that even these preparations cannot be guaranteed to effect absolute cure, except in the earliest stages of the disease, it is now well established that a considerably larger proportion of cures can be effected by salvarsan and its allies than by any other form of treatment.

By ' absolute cure ' is meant the complete eradication of the virus of syphilis from the body. To achieve such eradication it is necessary to administer the drug in doses as large as possible without undue risk, and a dosage which is large enough to be adequate, yet not so large as to endanger life or health except in a very small minority of patients, has been arrived at by the experience of twelve years.

There are, and there will always be, certain exceptional individuals who will react to the drug more severely than others and in whom a dose, or series of doses, harmless to the average man, may set up dangerous or even fatal complications. The scrupulous physical examination of a patient enjoined upon the practitioner before administration of salvarsan or its substitutes is designed to eliminate cases in which danger might arise, so far as this is possible by human skill and care. But there will remain a few individuals in whom, either from congenital intolerance or from the presence of disease which cannot be detected, such risk is unavoidable.

The data which have been presented in this Report afford some

indication of the proportion of individuals in which this is the case. It would appear that, with skilled administration, the proportion of fatal accidents should not be greater than 1 in 5,000 to 10,000 patients treated. If the accidents attendant upon intensive treatment in military hospitals during the war be disregarded it would seem that, with increasing experience, the proportion of fatal accidents is decreasing.

The patient who is suffering from syphilis, and the doctor who proposes to treat him, have to choose between two risks. On the one hand is the more or less measurable risk attendant on the arsenobenzol treatment which offers the most hopeful prospect of cure ; on the other the risks, that cannot so accurately be measured, which may attend uncured syphilis. The latter risks may attach not only to the patient, but to his wife, his unborn children, and to the community as a whole. It is, of course, right that the patient should have the facts clearly before him and make his own choice.

The Committee have no doubt that, in the interests of the patient himself, no less than in those of the community, the choice should be in favour of arsenobenzol treatment. They believe that the very small number of unavoidable deaths due to this treatment are immeasurably outweighed by the deaths and disabilities which would arise if the older methods of treating syphilis were alone practised. At the same time, the facts which have been brought together in this Report no less strongly emphasize the importance of the most scrupulous care in the administration of a drug which is necessarily employed in doses not far removed from the danger line.

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MEDICAL RESEARCH COUNCIL

No. 67

REPORT ON
ARTIFICIAL PNEUMOTHORAX

BY

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MEDICAL RESEARCH COUNCIL

INTRODUCTION

ACTING on behalf of the Tuberculosis Committee of the Council, Dr. Burrell and Dr. MacNalty have brought together the chief scientific and practical considerations that are now available for making judgement of the remedial value of 'artificial pneumo-thorax'—that method of treating disease of a lung by giving it controllable periods of rest from respiratory movement. The Council would here express their thanks to these authors for the thoroughness with which they have undertaken their task. In a matter of this kind, so vital to the interests of a large number of patients and of their medical advisers, it is of the first impor-tance that results of physiological experiment and of professional experience should be gathered as fully as possible, not only with a view to giving a proper basis of support for this operative procedure, but no less with a view to aiding the accuracy by which the most suitable cases for the treatment can be recognized and selected. It will be seen that the authors have been able to enlist the co-operation of a number of physicians with practical knowledge of this method who have been good enough to present in detail the results of their varied experience. To all these, and to others whose names are also given in the Report, the Council would desire to express their heavy indebtedness. They are confident that the usefulness of this joint contribution of experience will be widely recognized in the profession. It is plain that it must tend greatly to stimulate advances in our scientific knowledge of this subject, and it can hardly fail to lead to a more general and a more secure adoption of this method in the treatment of pulmonary disease.

21 *June* 1922.

MEDICAL RESEARCH COUNCIL,
    15 York Buildings,
        Adelphi,
            London, W.C. 2.

REPORT ON ARTIFICIAL PNEUMO-THORAX.

PART I.

REPORT ON THE VALUE OF TREATMENT OF PULMONARY DISEASE BY ARTIFICIAL PNEUMOTHORAX.

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Physician to the Brompton Hospital for Consumption and Diseases of the Chest.

CONTENTS OF PART I.

Preface.

In Part I of this Report I have described the results of my experience in treatment by Artificial Pneumothorax. The technique of the operation, the dangers, difficulties, and complications which may arise and the limitations of the treatment are discussed.

The literature on the subject is now extensive and references are given to the writings of others, whose works and opinions are here reviewed.

Introduction.

Artificial pneumothorax is not a new method of treatment. In 1822 Dr. James Carson (1821 ; 1822)[1] of Liverpool suggested its use in the treatment of disease, and the year previously he made a series of experiments showing the effects of artificial pneumothorax on the circulation. It was noticed that patients in whom spontaneous pneumothorax occurred did well, but little is heard of artificial pneumothorax until the end of last century. Cayley treated a case of haemoptysis at the Middlesex Hospital by this means in 1885, and about this time Forlanini began to use the treatment in Italy. It was not, however, until the beginning of this century that it became at all extensively practised. Gradually it became known, until now it is recognized as a valuable method of treatment by all who study diseases of the lungs. In 1909 Dr. Lillingston (1913), then a patient at Mesnalien Sanatorium in Norway, was treated by Dr. Holmboe by artificial pneumothorax. Although he had been ill with febrile pulmonary tuberculosis for over two years, Dr. Lillingston rapidly improved and returned to work in England in 1910. In August of that year he induced an artificial pneumothorax on a patient at Mundesley Sanatorium with Dr. Vere Pearson and Dr. Snowden and the patient made a good recovery.

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[1] *Note.*—The numbers in brackets refer to the dates of publication of the authors' articles on the subject. References will be found at the end of Part I, page 56.

Too little is known about artificial pneumothorax in this country, and many physicians regard it as a method of treatment which has been found wanting instead of one which has slowly but surely spread and established itself all over the world. It is true that any one who uses a special method of treatment is liable to be biased in its favour, but we find other methods of treatment, such as tuberculin, taken up and dropped. It is not so with artificial pneumothorax. I know of no one who has tried it seriously, and then discarded it. Adverse opinion is often based on hearsay alone, or comes from those who have seen only one or two cases.

It is a long method of treatment, trying both to the patient and physician. To have a series of patients with their frequent refills means days of hard and unbroken work. Success or failure of the treatment depends on care and strict attention to detail. Each patient must be taken individually and there can be no rule of thumb as to pressures, quantity of gas given, or spacing of refills.

I do not suggest that this method of treatment is the only one for pulmonary tuberculosis, and it certainly has its limitations, but in selected cases it gives a very good chance to patients who can expect nothing from any other form of treatment. It is also of the greatest value in certain non-tuberculous cases.

Sir James Kingston Fowler, at the Royal Society of Medicine on 24th May, 1921, said that he had lived to see two real advances in the treatment of pulmonary tuberculosis, one sanatorium treatment and the other artificial pneumothorax.

It seems to me to be very important to bring before the profession the possibilities of artificial pneumothorax ; more especially I hope that the treatment may be honestly and thoroughly considered by the great body of medical practitioners who see pulmonary tuberculosis in its earlier stages. Too often we see a patient in the very last stages and ask ourselves whether artificial pneumothorax or any other form of treatment might not have arrested or at any rate delayed the progress of the disease. For the most advanced case has usually passed through a stage when artificial pneumothorax would have given a genuine chance of recovery.

Chapter I.
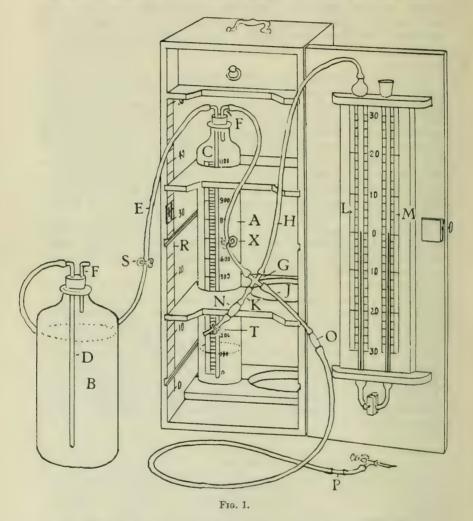
The Apparatus and Gas suitable for inducing Artificial Pneumothorax.

There are several forms of artificial pneumothorax apparatus. A simple and satisfactory apparatus is that devised by Drs. Lillingston and Pearson. Fig. 1 shows this instrument with a few modifications. It consists of two bottles a and b. a is graduated from 0 to 1,100 c.cm. and is tall and narrow, so that the graduations are easily read. Both bottles are fitted with rubber stoppers. A glass tube c passes through one stopper to the bottom of bottle a, and a similar glass tube d passes through the other stopper to the bottom of bottle b. These two tubes are connected by a

rubber tube E. Shorter glass tubes FF pass just through both stoppers.

Now if one bottle and the tubes C, D, E, are filled with water, the water will flow into the other until it is at the same level in the two bottles. Air will enter through the tube F in the empty-ing bottle and be forced out through the tube F in the other

Fig. 1.

bottle. Tube F from bottle A is connected by a rubber tube with one limb of a cross-shaped glass tube G. The three other limbs of this glass tube are fitted with rubber tubes, one of which, H, is connected with the manometer, another, J, is connected with the needle, and the third, K, is a short tube used only for filling the apparatus with air.

If the tube K is clamped and the bottle B raised so that water flows into A, the air in A will be forced out through the needle at

the end of tube J, but if J is clamped the air will force down the column of liquid in the left limb, L, of the manometer, and the liquid in the right limb, M, will rise.

If now the tube E is clamped so that no liquid can pass from one bottle to the other, J is unclamped, and the needle is put into the pleural cavity, a negative pressure will be indicated by the column of liquid in L being drawn up, and a positive pressure by it being forced down. N, O, are filters of sterilized cotton wool. P is a short glass tube in the tube J near the needle. R is a scale by means of which the difference in the levels of the liquid in A and B can be seen and the pressure of water determined. S, T, X are clamps.

When the apparatus is not in use the end of the tube J is closed by a glass rod. The tubing can easily be sterilized by boiling. It is important to see that the various connexions are sound and that there is no leak. This can easily be tested by making a small negative or positive pressure recorded on the manometer and after clamping the tubes seeing if any air escapes. Tubing of small bore should be used. If instead of entering the pleural cavity the needle enters a vein or pleural effusion, the blood or liquid will pass up the needle and be seen in the glass tube P.

The limbs of the manometer should be long and fitted with bulbs at the top so that the liquid may not be forced out of M by a high positive pressure or of L by a negative one. I use water coloured with a little red ink for the manometer liquid, mercury is too heavy. Some physicians use spirit, as it is lighter than water.

Dr. Clive Riviere uses bromoform, which has a specific gravity of about 2·830, and is not too heavy to prevent oscillations from being easily seen. Consequently the limbs of his manometer are much shorter, and his apparatus, which he was kind enough to show to me, is most ingeniously packed into a microscope box and is very portable. It is of the same type as the Lillingston-Pearson apparatus.

In order to use the apparatus bottle B is filled with 1 in 100 carbolic solution slightly coloured to make it more visible. A little air is blown with a Higginson syringe through F in bottle B to force the liquid up tubes D, E, C into bottle A in order to start a siphon action. When the liquid reaches O in bottle A the tubes E and K are clamped. J is clamped at X so that the needle is in connexion only with the manometer. The trocar is removed from the needle, and the tap at the top turned off. Clamps S and X are now unfastened and the end of the needle is put into a little methylated spirit, through which bubbles of air should pass if the apparatus is working properly. The needle is now dried over a spirit flame while about 200 c.cm. of air are allowed to pass, when clamps X and S are again fastened. Before using the apparatus the level of the liquid in A should be about equal to that in B, so that when E is unclamped the pressure in the tubing is atmospheric or even slightly negative and air cannot be forced out of the needle under pressure, and possibly cause air embolism.

Before using the apparatus it should also be tested to see that there is no leak by seeing whether a positive or negative pressure in the manometer remains constant when the tubes are clamped.

Dr. Parry Morgan (1914) has designed an apparatus with two manometers. He points out that with a single manometer it is not possible to take the pressure in the gas chamber and the intra-pleural pressure at the same time. Moreover, that when the gas is flowing the manometer shows practically only the pressure in the gas chamber with very slight respiratory oscillations, since it is connected with the pleural cavity by a small needle, and with the gas chamber by a tube of considerable bore. When the needle enters the pleural cavity a negative pressure is registered, but during expiration the visceral pleura will tend to block the orifice of the needle and a further negative pressure will be recorded during the next inspiration, so that the manometer is in fact a minimum pressure manometer. As gas is not allowed to flow until free oscillations are seen the visceral pleura is liable to be injured and the needle to become blocked. Moreover, when the oscillations have appeared and the gas is turned on, it is not possible to see whether the flow of gas continues except by watching the level of liquid in the two bottles. If the visceral pleura is injured and air escapes from the alveoli then oscillations occur unless the needle is blocked. With the double manometer these objections are overcome and it is also possible to see from the manometer whether or not the needle is blocked. There are undoubtedly advantages for this double manometer, but I have always found the single manometer quite satisfactory.

There are several other types of apparatus. Morriston Davies (1919, p. 165) uses one in which the bottles are fixed, the gas is forced out by water pressure, and the rate of flow regulated by a tap above the water cylinder.

The apparatus used by de Carle Woodcock (1913) is more complicated; nitrogen is manufactured and the bottles move up and down on rods. Lister (1915) uses a similar apparatus, but oxygen also can be generated.

Marshall (1921) has described a modification of the apparatus used by Professor Morelli, of Pavia. The gas is contained in a rubber bag, from which it is at first drawn into the pleural cavity by the negative pressure and later forced in by gently squeezing the bag. This apparatus has the advantage of portability, but does not register the exact quantity of gas used, nor the pressure at which the gas is introduced.

There are several types of needle used for producing pneumothorax. For the initial operation Clive Riviere's needle is very satisfactory. It consists of a trocar and cannula. When the needle has passed through the superficial tissues the trocar is withdrawn and the cannula, which has a blunt end, is pushed through the parietal pleura. There is, therefore, little danger of injuring the lung. It is illustrated in Figs. 2 and 3 (p. 19).

For the refills I always use Saugman's needle. In choosing a needle I should avoid one with too small a bore, as the movements

of the manometer are not so readily registered with small-bore needles. All pressures in my series are in cm. water.

Choice of gas.

Webb, Gilbert, James, and Havens (1914) made a thorough investigation and analysis of the gases in the pneumothorax cavity. They conclude, 'little, if any, advantage is to be gained by the employment of nitrogen rather than atmospheric air for the production of artificial pneumothorax'. They found on analysis of so-called pure nitrogen from a cylinder obtained from a commercial house that the gas contained N_2 86·02 per cent., O_2 13·98 per cent., CO_2 none. They therefore made their own oxygen and nitrogen.

They give the following tables. In each case 30 c.cm. of gas were withdrawn for analysis before a refill.

With Nitrogen.	In-jection.	Amount of gas given.	Analysis						Pressure	
			Of gas removed.			Of gas given.			before.	after.
			O_2	CO_2	N_2	O_2	CO_2	N_2		
20th Sept. 1913	1	400 c.cm.	—	—	—	4·25	1·64	94·1	−2	−2
22nd ,,	2	600 ,,	8·66	6·55	84·79	0·15	0·52	99·33	−2	−2
24th ,,	3	700 ,,	4·08	6·74	88·58	0·15	0·92	98·92	0	+1
29th ,,	4	800 ,,	3·08	7·26	89·66	0·1	0·61	99·29	0	+2
6th October	5	300 ,,	1·91	8·11	89·98	0·31	0·13	98·56	0	+2
15th ,,	6	400 ,,	1·31	9·02	89·67	2·75	0·41	96·84	0	+3
31st ,,	7	800 ,,	1·51	8·01	90·47				0	+4
With Atmospheric air.										
16th July 1913	1	200 ,,	—	—	—	20·93	0·03	79·04	−2	−2
17th ,,	2	300 ,,	7·92	6·85	85·23				−3	0
18th ,,	3	500 ,,	6·64	7·82	85·54				−2	0
21st ,,	4	800 ,,	4·17	7·08	88·75				−2	+1
26th ..	5	800 ,,	2·15	7·83	90·02				−1	+1
2nd August 1913	6	1,000 ,,	2·31	7·47	90·22				0	+2
11th ,,	7	1,100 ,,	1·97	8·00	90·03				−1	+3
21st ,.	8	1,250 ,,	2·28	8·20	89·52				−1	+4
2nd Sept. 1913	9	1,250 ,,	1·86	8·33	89·81				0	+5
16th ,,	10	1,400 ,,	1·58	8·28	90·14				−1	+4
6th October	11	1,200 ,,	2·35	8·7	88·95				0	+5
With Oxygen.										
1st December	1	500 ,,	—	—	—	95·56	—	—		
3rd ,,	2	900 ,,	24·04	4·16	71·8					
8th ,,	3	1,200 ,,	19·77	4·53	75·7					
11th ,,	4	1,000 ,,	21·76	2·64	75·4					

In the case of oxygen it is seen that nitrogen is diffused into the pleural space, and it must have come from the alveoli, since there is only about 2·4 per cent. nitrogen in the blood. It would seem that whatever gas is used nature changes it towards alveolar air. Rist and Strohl (1920) concluded that there is a balance between the gases of the pneumothorax cavity and the gases in the venous blood. When either air or nitrogen is introduced there follows a short period during which the total gas in the pneumothorax cavity is increased before interchange of gases establishes the balance.

Tobiesen (1911), of Copenhagen, found on analysis N_2 90 per cent., CO_2 6·7 per cent., O_2 3·4 per cent. in the pneumothorax

cavity, whether nitrogen, carbon dioxide, or oxygen had been used at the previous refill.

Sir William Ramsay (Morriston Davies, 1919, p. 54) analysed the gases in Morriston Davies's case of pyopneumothorax. He found N_2 95·45 per cent., CO_2 4·55 per cent. After 1,250 c.cm. of gas and liquid had been removed and been replaced by 750 c.cm. of oxygen, he found N_2 74·09 per cent., CO_2 4·35 per cent., O_2 21·56 per cent. Eight days later the pleural cavity contained N_2 98·13 per cent., CO_2 1·18 per cent., O_2 0·69 per cent. After replacing gas and liquid by 1,150 c.cm. O_2 he found N_2 76·34 per cent., CO_2 2·95 per cent., O_2 20·71 per cent.

With regard to the rate of absorption, nitrogen is perhaps absorbed slightly less readily than air. Oxygen is absorbed more quickly. Oxygen is therefore the best gas to use if a rapid absorption is required, as, for instance, in certain cases of pleural effusion.

Helium has been used in America by the late Dr. Paterson, of Saranak Lake, N.Y. It was found to have no advantages over air or nitrogen, and to be just as quickly absorbed. Some physicians use carbon dioxide at the initial operation, as it is more quickly absorbed by the blood (Grass, 1921). Personally I think air is the best gas to use for ordinary pneumothorax work as it approaches most nearly to the alveolar air, and therefore less interchange of gas is required. But really it matters little whether nitrogen or air is used. The difference, as an American said, is only a matter of dollars.

With regard to oxygen being beneficial to the patient, I have seen no evidence of this. Some physicians use oxygen at the beginning of the initial operation as a protection against gas embolism. I do not myself think this is necessary, and discuss the matter in a later chapter.

The following tables illustrate the rate of absorption of nitrogen and air :

Clive Riviere's case (1917, p. 33) at three-weekly intervals :

3rd January	$-10-1$	620 N_2	$-4+5$
22nd ,,	$-10-0$	660 N_2	$-5+5$
11th February	$-10-1$	600 N_2	$-4+5$
3rd March	$-9-1$	560 N_2	$-4+5$
24th ,,	$-8-0$	460 air	$-4+5$
14th April	$-7+1$	400 N_2	$-4+5$
5th May	$-8+1$	490 N_2	$-3+6$
26th ,,	$-8-0$	520 air	$-3+5$
16th June	$-8-1$	560 N_2	$-5+5$

In one of my cases at four-weekly intervals the pressures were :

7th April	$-8-2$	1,000 air	$+2+12$
5th May	$-8-2$	1,000 air	$+1+11$
2nd June	$-7-3$	1,000 N_2	$+2+11$
30th ,,	$-8-3$	1,000 air	$+1+11$

In another at three-weekly intervals :

10th March	$-6-0$	700 air	$+4+9$
31st ,,	$-6-1$	750 air	$+4+10$
21st April	$-5-0$	750 N_2	$+3+9$
12th May	$-6-0$	700 air	$+4+9$
2nd June	$-5-1$	700 air	$+4+8$

It should, however, be emphasized that the rate of absorption varies greatly in different cases. Gas is absorbed more rapidly in the early stages of pneumothorax treatment, and in my experience absorption is much more rapid in the acute and febrile cases than in chronic afebrile ones.

CHAPTER II.

THE SELECTION OF CASES.

For the purpose of artificial pneumothorax treatment, we may consider pulmonary tuberculosis under the following groups:

A. Patients with little or no powers of resistance. Here the disease rapidly spreads and proves fatal.

B. Patients with very good powers of resistance. Here the disease becomes completely arrested by sanatorium or other medical treatment.

C. Patients with a medium power of resistance, which may be fairly good with very few systemic symptoms, or rather bad with severer symptoms. This group may be subdivided into—1. The early stage where only one lung is involved. 2. The medium stage where there is involvement of the better lung, but less than a third as determined by clinical and X-ray examination. 3. The advanced stage where a third or more of the better lung is involved.

With regard to group A, I have induced artificial pneumothorax in a few patients, but they all died. The treatment generally did not seem to affect the course of the disease one way or the other. Cases of acute pulmonary tuberculosis have, however, been successfully treated by pneumothorax.

For patients in group B, artificial pneumothorax is not necessary, but they should be watched carefully to be certain that the disease really is arrested.

It is in group C that artificial pneumothorax is of such value, especially in the first or early stage. If a patient in this stage, after six months of medical or sanatorium treatment, still has signs and symptoms of active disease, and tubercle bacilli are still present in the sputum, I should always advise artificial pneumothorax. It is of the greatest importance fully to consider this point of view. In the first place I urge that one must not argue from individual or exceptional cases. In the great majority of cases in such a condition the disease progresses to a fatal termination, perhaps slowly when the disease takes on the so-called fibroid type, or perhaps more rapidly by a gradual and steady spread of the infection. If at the end of these six months great improvement has been made in spite of a few signs and tubercle bacilli still being present, some physicians may consider it wise to wait for a further period of about three months. One must remember, however, that patients invariably improve at first with sanatorium treatment, but in the majority of cases the

improvement is only temporary. What has to be decided in the interests of the patient is this: Is it better to risk any possible ill effects from artificial pneumothorax, or to risk the disease reaching that stage when the value of pneumothorax treatment is much diminished?

The risks of artificial pneumothorax are so small, and the chances of the disease spreading are so great, that I think all patients in this stage of the disease should at least be given the opportunity of pneumothorax treatment. In my opinion it is the only method of treatment which gives them any real chance of permanent benefit. The dangers of the treatment compared with those of the disease are discussed in Chapter VII.

In the second stage of group C we meet the type of patient who in most cases has been left too long. At the same time a great improvement usually follows pneumothorax treatment, and in some cases the disease actually becomes arrested. The effect of artificial pneumothorax on the other lung will be considered later.

In the third stage no good results can be expected from any method of treatment. It may be mentioned that pneumothorax on both sides may be considered both in this and in the second stage, but results obtained from this treatment are not often encouraging and will be discussed later.

In addition to pulmonary tuberculosis, artificial pneumothorax treatment is of great value in cases of one-sided bronchiectasis and abscess of lung.

It is impossible to give a list of the indications and contra-indications for artificial pneumothorax, for each case must be considered on its own merits. Speaking generally, however, it may be said that in the absence of any special contra-indication the following cases are suitable:

1. Any patient with a tuberculous lesion of one lung, who has signs of activity after six months' medical treatment.
2. Patients with tuberculous disease in both lungs, but with less than one-third of the better lung involved.
3. Recurrent or repeated haemoptysis as a result of tuberculosis or other disease of the lung.
4. Bronchiectasis if there are toxic symptons, with copious or offensive sputum. I should not advise pneumothorax in a chronic case of bronchiectasis if there were no systemic symptoms and little sputum.
5. Abscess of lung.
6. Pleural effusion. This may well be treated by replacing the liquid withdrawn with oxygen.
7. To stop pain in acute dry pleurisy (Morriston Davies, 1919, p. 39).

The contra-indications are:

1. Disease of one-third or more of the better lung.
2. Extensive tuberculous disease elsewhere, such as tuberculous enteritis. Tuberculous laryngitis is no contra-indication and is usually improved by the treatment.

3. When the pulmonary tuberculosis is a terminal infection or intercurrent with some general disease such as diabetes, cirrhosis of the liver, chronic nephritis, &c.
4. Patients with a highly neurotic temperament do badly.
5. Ill-nourished patients, patients with chronic dyspepsia, or severe visceroptosis.
6. Asthma and emphysema are not always absolute contra-indications, but pneumothorax should be performed in such cases only if there are special or urgent indications.
7. Patients with good resistance in the early stages of pulmonary tuberculosis should first be treated by ordinary medical methods.

It should be repeated, however, that each case must be considered individually, and that there is no golden rule as to the selection of cases.

<div align="center">CHAPTER III.</div>

<div align="center">THE PREPARATION OF THE PATIENT, AND TECHNIQUE OF THE OPERATION.</div>

The mental attitude of the patient is of the greatest importance. Patients who have confidence do best, and, indeed, I regard a high degree of nervousness as an actual contra-indication to pneumothorax treatment. In a hospital or sanatorium where several patients are having the treatment, other patients often ask for it themselves, and this is of the greatest help. In a private case, however, the patient is too apt to regard it as a new form of treatment, just worth risking as a highly unlikely last chance. A little dyspnoea becomes serious gasping for breath, or a feeling of tightness or a little pain may lead to alarming symptoms, which I have not seen in those who have confidence in the treatment. It is therefore very necessary to explain the treatment and get the interest and confidence of the patient.

Most cases treated are bed cases, but if the patient is up and about he should be kept in bed for the first week. After that, if there is no reaction, he may be allowed up between the refills, provided he rests for 12 hours after each refill until the lung is completely collapsed. It is better to have the patient in a nursing home for the first fortnight. If it is done at his home a trained nurse should be engaged for at least a week.

The evening before the treatment is started I order the patient calomel, to be followed by salts in the morning, and half an hour before the operation I inject a quarter of a grain of morphia or 1 c.cm. of a 2 per cent. solution of omnopon. Omnopon is less likely to cause vomiting. At the bedside ether, pituitary extract, and other stimulants should be in readiness in case of emergencies, and hot-water bottles should also be at hand.

The patient should be arranged comfortably in bed, supported by pillows, so that the site of the puncture is uppermost and the ribs in that region are as far apart as possible. The area selected

for puncture is then painted with iodine and surrounded by sterilized towels as for a surgical operation.

A hypodermic syringe is filled with 2 c.cm. of a 2 per cent. solution of novocain with a little adrenalin, and about ¼ c.cm. is injected intercutaneously over a rib, forming a swelling in the skin about the size of a threepenny-bit. The needle is then taken out and the skin pulled down so that the swelling is over an intercostal space. The needle is then inserted into the middle of the swelling and very slowly pushed between the ribs to the pleura, novocain being injected all the time and the last ½ c.cm. injected against the pleura. It should be quite painless except for the first prick made to anaesthetize the skin. The skin is drawn down so as to form a valve and be some protection against the formation of surgical emphysema.

The apparatus, which has previously been got ready and tested as already described, is then arranged at the patient's bedside. Some operators incise the skin with a tenotome before putting in the pneumothorax needle, and it is said that this prevents organisms being carried into the pleural cavity from the skin, and also prevents the possibility of the skin offering resistance and necessitating force to introduce the needle, which might go with a jerk against a sensitive rib or into the lung. But the use of a tenotome makes a dressing necessary, leaves a scar, and often a little sore which is irritating to the patient. If the skin is properly cleaned there is no danger of infection, and provided the needle is sharp it passes quite easily through the skin which has been stretched over an intercostal space. I have never found it necessary to use sufficient force to make it possible for the needle to be jerked onwards after piercing the skin, and the only danger of striking a rib is if the patient makes a sudden movement, which should be prevented by properly anaesthetizing the skin.

A Clive Riviere needle attached to the pneumothorax apparatus is then dried in a spirit flame and pushed gently through the anaesthetized skin between the ribs until the pleura is reached. The trocar is withdrawn and the tap at the top of the needle is turned off. The cannula is gently pushed forward until its blunt end can be felt to have gone through the parietal pleura. The manometer will then show a negative pressure with oscillations corresponding to inspiration and expiration, which are noted. The patient must keep absolutely quiet and the needle be held perfectly steady in order to keep it in the pleural cavity. The connexion with the air-chamber is now opened and air allowed to be sucked into the pleural cavity until 50 or 100 c.cm. have entered. The bottle is then raised and about 300 c.cm. of air allowed to enter the pleural cavity. The readings of the manometer are then noted and the needle withdrawn. A little iodine is painted over the puncture, but no dressing is required. Some physicians (Woodcock, 1915) warm the gas before allowing it to enter the pleural cavity. The patient is usually drowsy after the morphia and should be allowed to sleep. No special restrictions of diet are required, but as he is in bed a light diet is best.

It is not always that everything goes as smoothly as in the straightforward case described above. As soon as the needle enters the pleural cavity a negative pressure is registered, but there are often little or no oscillations or the oscillations quickly stop. This is because the visceral layer of pleura tends to obstruct the end of the cannula. At first the small quantity of air in the needle and tubing is sucked into the pleural cavity and oscillations are seen, but this air spreads in the pleural cavity away from the needle, the end of which becomes obstructed by the visceral pleura. At first, during inspiration, the pressure becomes more negative, and at expiration the visceral pleura blocks the cannula: a valve action, which practically makes the manometer a minimum pressure one. Oscillations may start again owing to an injury of the lung allowing air to escape from the alveoli (Parry Morgan, 1917), but if care is taken and the end of the cannula is blunt this should not happen. If, therefore, it is assumed that the needle has slipped out of the pleural cavity because the oscillations stop, it may be that an unnecessary number of punctures are made on the patient or the lung may be pierced. When it is thought that the pleural cavity is reached by the original negative pressure and oscillations shown on the manometer, a little air should be allowed to be sucked in at once and the patient should not cough or breathe deeply. If, as usually happens, the oscillations increase and a negative pressure of at least 3 to 6 cm.[1] is registered, it is certain that the needle is in the pleural cavity. If, on the other hand, there are no oscillations when the connexion with the air-chamber is unclamped, the needle is not in the pleural cavity.

By this method there is no danger of air embolism. In the first place air is not leaving the needle under a positive pressure, but only a very small quantity is being sucked out. Secondly, the patient is not allowed to cough or breathe deeply. The chief reason for giving morphia or omnopon is to keep the patient quiet. Thirdly, if the needle is in a vessel the blood will be seen in the glass tube just above the needle, unless it is clotted in the needle, in which case there is no danger. Lastly, by using a large-bore and blunt Clive Riviere needle there is very little danger of piercing a vessel.

There are certain movements of the manometer which do not indicate that the needle is in the pleural cavity. A few small oscillations may be seen when the needle is against, but has not pierced, the parietal pleura. When the needle enters the lung a negative pressure, becoming greater with each inspiration, but no oscillations, may be noted. The needle usually becomes blocked very soon by clotted blood. Oscillations a point or so above and below zero are seen when the needle is in a cavity or bronchial tube. I have heard of a case in which 2,000 c.cm. of gas were introduced with no alteration in the reading of the manometer, which showed small oscillations round about zero all through the operation. In this case it is obvious that the needle was not in the pleural cavity at all, but that the gas was passing

[1] All pressures unless otherwise stated are in cm. water.

out through the bronchial tubes. In one of my cases of bronchiectasis the manometer showed these small oscillations and I took it that the needle was in a bronchial cavity. After putting a little peppermint on some cotton wool, holding the wool over the top of the needle, and turning on the tap of the needle, the patient was able to taste the peppermint.

It sometimes happens that the pleura is much thickened and adherent, and it feels as if one was pushing the needle through cork. In such cases it is seldom possible to produce a satisfactory collapse.

If the needle goes into a pleural effusion there will be no oscillations of the manometer, but a negative or positive pressure may be registered and liquid may be forced up the tubing. If, however, it is in the air-space above the effusion a considerable negative pressure is usually registered, but this becomes positive after the introduction of a very small quantity of gas.

In a straightforward case, therefore, about 300 c.cm. of air may be given, and it is found that the original negative pressure in the pleural cavity is slightly less negative. For example, $-12-8$ altered to $-10-7$ by 300 c.cm. Or $-7-4$ to $-4-2$ by 300 c.cm. In some cases, however, a very small quantity of air makes a great difference in the intra-pleural pressure. This is usually because the needle is in a pocket shut off from the rest of the pleural cavity by adhesions. Indeed, after one or two refills one can get a rough idea of the amount of collapse likely to be obtained in a case by noting the pressures.
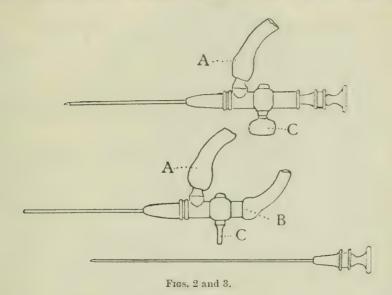
If a big positive pressure is obtained with very little air, the case should be treated as if the pleural cavity had not been reached and an attempt made elsewhere. In one such case I found a pressure of $0-4$ was converted into $+19+23$ by 150 c.cm. of air. In another case $-6-8$ was converted into $+2+4$ by 300 c.cm. In the first case I tried another site. In the second I kept on at the same site, but was able to induce only a very partial collapse. If it is not possible to find the pleural cavity at the first attempt, I try once more at some other site; if that fails I wait until the next day, when I make two more attempts. If they fail I do not continue, because I believe that if the visceral and parietal pleura are adherent in four different places it is not possible to induce a satisfactory pneumothorax. As already explained, the choice of site must vary with the position of the disease, but common sites to try in a case of failure in the mid axillary line are over the base of the lung at the back, the posterior axillary line, and the second intercostal space below the clavicle.

When Forlanini first used the treatment he had no manometer and the needle had gas escaping under pressure as he pushed it through the parietal pleura into the pleural cavity. If the needle was in the pleural cavity the gas flowed freely, and this was the only way of knowing whether or not the pleural cavity had been reached. Murphy (1898), in America, used the same method. At that time gas embolism was occasionally produced by the gas getting into the circulation.

Brauer, in Germany, advocated producing artificial pneumo-
thorax by the open method in order to avoid injury to the lung
and to prevent gas embolism. He used to incise the skin and
superficial structures and expose the parietal pleura. He would
then put the needle into the pleural cavity and introduce the
gas.

When pneumothorax is induced to replace a pleural effusion
the operation is slightly different. The patient should lie on his
side with the axilla of the affected side uppermost, and a Riviere
needle attached to the pneumothorax apparatus is put into the
pleural cavity in the 4th or 5th intercostal space, just in front
of the latissimus dorsi. If there is an air-space the needle will
be in it with the patient in that position, and the oscillations of
the manometer will be seen. If the needle is in the effusion

Figs. 2 and 3.

there will be no oscillations, but they will appear if a little air is
allowed to leave the needle and form a small air-space. The
rubber tubing is clamped just beyond the needle and a second
and larger needle is put through the back into the effusion.
Air or oxygen is then allowed to enter from the pneumothorax
apparatus through the top needle, and the liquid flows out
through the other one. By this means all the liquid can be
replaced by gas without any change in intra-pleural pressure.

If the pleural cavity is to be washed out with saline or some
other solution, the procedure is the same, except that when the
Riviere needle (Fig. 2) has been inserted into the pleural cavity,
the trocar withdrawn into the stuffing-box, and the tap (c) turned
off, the top of the needle is removed (Fig. 3) and a rubber tube
fitted to the needle at B. This tube is connected with a funnel
through which saline can be introduced. When as much liquid
as possible has been removed through the larger needle in the

patient's back and replaced by a small amount of oxygen from the pneumothorax apparatus through tube A, this tube (A) is clamped near the needle, the tap C is turned on, and saline introduced from the funnel through the tube B. Thus the pleural cavity is washed out, the liquid leaving the cavity through the larger needle in the back. The position of the patient should be slightly changed once or twice during this operation, so that the saline and effusion may be thoroughly mixed. When the liquid from the pleural cavity is quite clear the tap C is turned off, the remaining liquid in the pleural cavity drained and replaced by oxygen introduced through tube A. At the end I leave a negative intra-pleural pressure of about 6.

Chapter IV

Reinflations and Termination of the Treatment.

It is largely on careful spacing of the refills that success or failure of the treatment depends.

It must be remembered that the lung collapses by its own elasticity, so that in the early stages of the treatment we are letting the lung collapse by allowing air to enter the pleural cavity. When atmospheric pressure is reached, however, we compress the lung by forcing in more air.

It is better to allow the lung to collapse gradually, for not only is there a danger of reaction from auto-inoculation, but by pressing out secretions the other lung may become infected. I always give small doses at the beginning of the treatment, and believe this to be the practice of most operators, but formerly large doses were given. In cases of severe haemoptysis I have given a large first dose, for, in order to check the haemorrhage, it may be necessary to risk the possibility of any ill effects. Personally I have not seen any permanent ill effects in any of these cases, but I certainly do not advise a large first dose unless the haemoptysis is really urgent. Chart I shows a big reaction following an initial large dose, but the patient had no more haemoptysis, and now, eighteen months later, is still under treatment but at work, with no sputum and no tubercle bacilli in the last examination.

As a rule, then, we may take 300 c.cm. to be the initial dose. If this is followed by a reaction I should repeat the dose as soon as the reaction had subsided. If there is no reaction I should give 400 c.cm. the next day, and 400 or 500 after another 48 hours. The following cases give some idea of the treatment during the early stages :
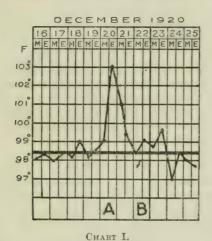
I.	18th July	−6 − 4	300 c.cm.	−5 − 2
	19th „	−6 − 4	400 „	−5 − 1
	21st „	−6 − 2	500 „	−4 − 1
	24th „	−5 − 2	500 „	−4 − 0
	27th „	−4 − 2	500 „	−2 − 0
	31st „	−2 − 1 ·	500 „	−1 + 1
	5th August	−4 − 2	600 „	+1 + 4
	12th „	−4 − 1	600 „	+2 + 4
	22nd „	−3 − 0	600 „	+4 + 7

II.	2nd February	−14−10	300 c.cm.	−10−4
	3rd ,,	−12−8	400 ,,	−8−2
	5th ,,	−8−4	450 ,,	−6−0
	8th ,,	−9−2	500 ,,	−4+2
	12th ,,	−8−1	600 ,,	+0+5
	16th ,,	−6−0	650 ,,	−1+6
	23rd ,,	−3−0	600 ,,	+2+8
	4th March	−2+1	600 ,,	+4−9

These two cases are straightforward, and offer a good chance of satisfactory results.

Dr. Wingfield tells me that he does not think it necessary to give but a small initial dose, provided there is no great change of intra-pleural pressure or alteration in the pulse or general condition of the patient. He never raises the pressure more than

CHART I.

A. Initial operation, 1,400 c.cm. of air introduced.
B. First refill, 1,200 c.cm. of air introduced.

2 c.cm. of alcohol at the initial operation, and only 1 c.cm. if there is any distress, but he finds that in cases without adhesions it usually takes 600–800 c.cm. of air to do this.

I used to give a larger initial dose than I do now, and I must repeat that I have never seen any ill effects from this practice, even when a really large dose (such as 1,500 c.cm.) is given. But it is more rational to be guided, as Dr. Wingfield suggests, by the intra-pleural pressure and general condition of the patient than to take some fixed quantity such as 300 c.cm. as the initial dose. Again, I agree with him that one would not expect (nor in his experience and mine do we find) any different result to the patient whether 100 c.cm. or 600 c.cm. are given, provided the intra-pleural pressure is only slightly raised—that is to say, provided the lung is allowed to become partially collapsed by its own elasticity and not compressed.

In spite of these reasons, however, I do give a small initial dose now, because I see no advantage in giving a larger one. The initial operation is not only the most difficult, but the most

distressing for the patient. The sooner it is over the better. 300 c.cm. of air are quite enough to leave an air-space into which the first refill may easily be made. If the patient gets over the initial operation without any pain or subsequent discomfort or dyspnoea, it is greatly to his advantage. He does not dread the refills, and I believe the mental attitude of the patient to be of the greatest importance. I certainly should advise any one starting the treatment to use small initial doses. Large doses without strict attention to the pressure and the patient's condition are to be condemned.

After about the first month one tries to find the correct spacing of the refills and the optimum pressure for each individual, and for this purpose the X-ray is very useful (see Chapter XI). In the majority of cases in which the collapse is satisfactory it will be found that the temperature has fallen to normal and that the cough and sputum are much less. In these cases the spacing of the refills is gradually lengthened from 7 days to 10, and then 14, then 17, and then 21. If it is found that the patient can go three weeks between the refills with no rise in temperature, increase in sputum, or other symptoms, I keep to this interval for six months at least. After the first month of treatment about 200–250 c.cm. of air are absorbed weekly, so that from 600–800 c.cm. of air are required every three weeks. As the treatment goes on, the air is absorbed rather less quickly.

One cannot lay down a rule as to spacing of refills, for each case must be considered individually. For instance, if it has been decided to leave 17 days between the refills, but on the 15th day symptoms, such as increase of sputum, occur, the refill should be given at once. One should try again to leave a 17-day interval, and probably it will be possible to do so the next time. It is usually possible to get to a three-week interval after the second month. If the patient is found to be comfortable and doing well with a pressure raised to, say, + 4 + 8 every three weeks, this pressure should be reached each time. If, on the other hand, a greater or lesser pressure suits the patient, this should be reached and the interval between the refills determined. For the first six months I think intervals of longer than three weeks are not advisable; at least, in my best results, about that interval between refills has been left after the second month. The optimum pressure may vary as time goes on. In a good case it is not uncommon to find it falls when the treatment has been going on for some months.

At the end of the sixth month it may be possible to increase the interval between the refills to a month, but personally, if all is going well, I keep to the three-week interval until the end of the first year. During the second year I try, and usually succeed in getting, the interval increased to a month, and after the second year the interval may be six weeks or even two months.

Large doses at long intervals during the latter part of the first and early part of the second year may give good results. In one of my cases a man who could attend only once in six weeks had a refill every six weeks from the sixth month of treatment until

the end of the second year. At each refill he had from 1,000 to
1,400 c.cm. He did very well and is now at full work and free
from symptoms. But patients usually complain of tightness and
discomfort just after a large refill, and of some return of symptoms
before the refill if the interval is so long.

In a straightforward case, therefore, I may say—

1. That the lung should be allowed to collapse gradually.

2. That when it has been collapsed the optimum interval
between refills and the optimum pressure should be determined
for each individual case. This optimum pressure may vary in
individual cases, so the condition of each patient must be under
constant consideration.

3. In my experience—certainly for the first year of treatment—
a moderate quantity of air given at not too long intervals gives
better results than a large quantity at long intervals.

One has to decide when to stop the treatment in a straight-
forward case which is doing well. Professor Saugman (1920)
writes : 'The pneumothorax being complete, I now normally let
the patient be treated for about five years. If then all is normal,
and if he wishes it, I let the pneumothorax close, choosing the
summer season to allow the lung to re-expand, for the first
months observing the patient very closely, if possible in the
sanatorium ; and no sooner do symptoms of relapse in the treated
lung appear than I renew the injection of gas, but only in a very
few cases have I seen reason to do so.'

He gives the following table :

Of 44 patients discharged 1907–17 and at work in 1919, com-
pression has lasted :

$\frac{1}{2}$ year in 1 case.	2 to 3 years in 17 cases.	5 to 6 years in 1 case.
$\frac{3}{4}$ to 1 year in 2 cases.	3 to 4 years in 7 cases.	6 to 7 years in 1 case.
1 to 2 years in 11 cases.	4 to 5 years in 2 cases.	Unknown in 1 case.

Professor Saugman has found relapse after effective treatment
to be very rare. He has had only six cases and in two of them
the treatment had to be broken off too soon.

Relapse showed itself six months after the treatment ceased in
two cases, 1 year in 1 case, 2 years in 1 case, 3 years in 1 case,
and 4 years in 1 case.

Dr. Vere Pearson (1919) states that in his opinion the compres-
sion should be kept up for at least three years if it is effective.
He would continue the treatment with an occasional refill for
a further 18 months—1. If the patient is over 33 years and has
lost the resilience and recuperative powers of youth. 2. If the
compressed lung was a fairly useless one before the initial injec-
tion, and if in addition it was producing chronic poisoning. 3. If
things are going well during the maintenance of the compression.

In my opinion three years should be the minimum. After that
the lung can be allowed to re-expand gradually by giving less
air and allowing longer intervals between the refills : the patient
being observed carefully, including X-ray examinations, and on
any return of symptoms the compression is continued. If all
goes well during the re-expansion it should be allowed to take
about 12 months. That is to say, a four years' treatment in all.

It must be remembered that as the lung expands the visceral pleura usually becomes adherent to the parietal pleura, until gradually the two are completely adherent, and no further pneumothorax is possible, although good results may sometimes be obtained by thoracoplasty.

I have often been asked by patients to continue the treatment when for some reason I have not been able to do so. The patient has a sense of security whilst under treatment and the inconvenience is very slight. One woman told me she much preferred having a refill to going to her hairdresser.

Chapter V.

Adhesions.

So far we have dealt only with straightforward cases that have been doing well, but in many cases the treatment has to be stopped for one or other reason in the early stages.

The visceral and parietal pleura may be so adherent that it is impossible to produce any pneumothorax at all. There may be adhesions sufficient to prevent an effective pneumothorax, or the adhesions may not be extensive, so that in spite of them a satisfactory pneumothorax may be induced. Of 196 cases I failed to produce any pneumothorax in 25 cases (12·7 per cent.) ; of 171 cases in which I did produce a pneumothorax, I had to stop the treatment in less than two months, owing to adhesions, in 21 cases.

	Failure to initiate an artificial pneumothorax.	Failure of pneumothorax owing to adhesions, complete or partial. (This includes the figures in the first column.)
Clive Riviere	20 per cent.	37 per cent.
Saugman	11 ,,	22 ,,
Zink	24 ,,	27 ,,
Hamman and Sloan	15 ,,	—
Keller	12·5 ,,	37·5 ,,

These results of course depend on the class of case treated (Riviere, 1917, p. 52).

As an example of an extreme case in which some air could be introduced, I may mention a man in whom I failed to find the pleural cavity at the first attempt. At the second I found a space with pressure 0−4, but by giving 150 c.cm. of air the pressure was +19+23. The next day I tried in a different place and failed, but tried again elsewhere and found a pressure of −2−6, which was raised to +8+12 by 100 c.cm. of air. I did not make any further attempts to produce a pneumothorax.

In another case I found no benefit and there was practically no collapse of lung after 10 days, so I stopped the treatment. In this case the intra-pleural pressures were :

15th August	−6−3	300 c.cm.	0+2
16th ,,	−4−3	300 ,,	+6+8
17th ,,	0+1	200 ,,	+10+12
19th ,,	−1+1	300 ,,	+12+14
22nd ,,	0+1	300 ,,	+16+20
25th ,,	+1+3	200 ,,	+18+20

In another case, as shown in X-ray Plate I, only a partial collapse was possible and the optimum pressure $+18+22$ at three-weekly intervals. Gradually the pleural space became obliterated by the visceral and parietal layer of pleura becoming adherent, and the treatment, which was started in November 1919, had to be stopped in June 1921. During the treatment, however, the patient kept very well, and now, in November 1921, has no sputum and no symptoms except a little dry cough. He is at work, and his weight, which was 10·2 in November 1919, is now 11 stone. I have had no other case in which such a partial pneumothorax gave such a good result.

Adhesions form round the diseased parts of the lung, the very parts it is necessary to collapse. Sometimes these adhesions may stretch or even give way during treatment, especially if a high intra-pleural pressure is kept up. In my experience it is very rare to find this happen. In one case, however, a patient told me he had a feeling in his chest as if plaster was being stripped from a wall, and afterwards the feeling of tightness left from the refill completely disappeared. At the next refill it required 350 c.cm. more air to reach the same pressure. In another case I was able to lessen the symptoms by giving frequent refills and raising the intra-pleural pressure to $+16+20$ at each refill. The patient complained of feeling tight after each refill, and on one occasion she felt as if something had given way inside her chest, and the feeling of tightness disappeared. This happened in only three of my cases, and was probably due to adherent pleura or an adhesion being stripped from the chest-wall. One should remember, however, that when the intra-pleural pressure is high it may suddenly fall owing to shifting of the mediastinum. When large surfaces of the visceral and parietal pleura are adherent it is common for the adherence of the pleura to increase during treatment. If after a refill a partial pneumothorax is produced, one usually finds that before the next refill a little more of the pleura has become adherent, until eventually the pneumothorax cavity becomes obliterated. This is not an uncommon cause of having to abandon the treatment, although many such cases do very well, being left with a fibroid lung. I do not think the gradual obliteration of the pneumothorax cavity can be prevented, but the process may be delayed by giving frequent refills and keeping the intra-pleural pressure high. Dr. Lillingston (1918) describes a case in which the refills were being given once a month, but were left once for an extra two weeks, when it was found that 300 c.cm. of gas caused a pressure of $+8$. Frequent refills were given and the pressure taken to $+16$, but the pneumothorax cavity became obliterated.

I do not think it wise to keep the intra-pleural pressure too high, and do not now use this method for dealing with adhesions. Indeed I feel strongly that any attempt to stretch or break away pleural adhesions by high intra-pleural pressures should be avoided.

Except when the collapse of lung is practically complete, I have usually found that the symptoms continue and the treatment has to be abandoned. In two cases in which adhesions were preventing

the proper collapse of the lung, I advised operation and the adhesions were cut. Both patients, however, died a few hours after the operation. In one case the pleural cavity was found to be full of blood from the severed adhesions. In the other it was found that the severed adhesions contained lung tissue and a large cavity. A quantity of pus poured into the pleural cavity, and the patient died from shock.

It is not uncommon to find lung tissue in an adhesion, and this should be suspected in a case where the lung is fairly well collapsed, except where drawn to the chest-wall by an adhesion, and the symptoms continue. High intra-pleural pressures in such cases are especially dangerous, as they may lead to rupture of the lung and a consequent pyopneumothorax.

If there is one large definite adhesion which prevents a sufficient collapse of lung, I think it would be better to free it by cutting the parietal pleura round the adhesion and allowing this part of the parietal pleura to remain with the collapsed lung, instead of cutting the adhesion itself.

If, however, there are extensive adhesions or a large part of the visceral and parietal pleura are adherent, I should advise abandoning the pneumothorax treatment and dealing with the case by some other method, such as collapsing the lung by injecting paraffin wax outside the parietal pleura, or by thoracoplasty.

In 1913 Professor Jacobaeus (1913, 1921) described a method of finding adhesions with a thoracoscope and dividing them with a galvanocautery. Dr. Holmboe (1919) has treated several cases in this way with considerable success. It is a difficult operation, however, and often very painful. There is, moreover, the danger of making a communication between the lung and pleural cavity and producing a pyopneumothorax, and some danger of haemorrhage. With the thoracoscope the nature of the adhesions may be seen. Some are small and flat, others thick round bands. It is very useful, therefore, to examine the pleural cavity with the thoracoscope before deciding upon the treatment of adhesions. Operations to free adhesions or collapse the lung are essential in cases where pneumothorax treatment is impossible owing to adhesions and the patient is becoming worse. Such operations, however, require the greatest skill, and good results can be expected only when the surgeon has had special experience in this work. Reference should be made to the book on Lung Surgery by Dr. Morriston Davies (1919, pp. 182–92).

In the case of an adhesion to the diaphragm causing pain or an irritating cough, division of the phrenic nerve may arrest the symptoms. I have had one successful case in my series.

Chapter VI.

Intra-pleural Pressure.

The intra-pleural pressure is registered by the manometer. It is found that mercury is too heavy to register the oscillations of respiration, so water or spirit is used.

The size of needle is of some importance, as the oscillations are not well shown if too small a needle is used. Of course the same actual mean pressure will be registered whether a large- or small-bore needle is used. If two needles (one being a large pneumo-thorax needle and the other an ordinary small hypodermic needle) are connected with the manometer by means of rubber tubes and a T-shaped glass tube, and are put into a distended rubber bladder, it will be found that the pressure registered through the small needle is the same as that registered through the large one, but it takes longer to register through the small needle. By giving the bladder little taps the manometer shows good oscillations if connected through the large needle, but hardly any movement if connected through the small one. Similarly, it will be found that if the liquid in one bottle of the pneumothorax apparatus is higher than the liquid in the other and the outlets are stopped, the column of water in the manometer will show the pressure, and it will be the same whether the tube to the manometer is fully patent or partially obstructed, but it will take longer for the pressure to be registered if the tube is partially obstructed. It is very important that the respiratory oscillations should be well shown, and for this reason the bore of the needle used should be at least 1·2 mm.

Normally the intra-pleural pressure is negative owing to the elasticity of the lungs, and becomes more negative during inspiration. It varies considerably in different individuals. It also varies with posture. This can be seen during pneumothorax treatment by making the patient change his position. The pressure is higher if the patient lies on his back than in the lateral position (Lawson, 1922).

As air is allowed to enter the pleural cavity the pressure approaches atmospheric pressure, and then if more air is forced in to compress the lung the pressure becomes positive.

The following table shows how the intra-pleural pressure rises as air is introduced:

	Case I. Initial operation.	Case II. Initial operation.	Case II. Three months later.
Initial pressure	−14 − 12	−7 − 5	−3 − 0
After 100 c.cm. air	−10 − 9	−7 − 2	−3 − 0
,, 200 ,,	−10 − 8	−7 − 2	−2 + 2
,, 300 ,,	−9 − 6	−6 − 2	+0 + 2
,, 400 ,,	−8 − 6	−6 − 1	+1 + 4
,, 500 ,,			+2 + 5
,, 600 ,,			+4 + 7
,, 700 ,,			+6 + 9
,, 800 ,,			+8 + 11
,, 900 ,,			+10 + 13
	Case III. Refill.	Case IV. Refill.	
Initial pressure	−12 − 8	−6 − 0	
After 600 c.cm. air	−3 − 0	—	
,, 700 ,,	−2 − 0	—	
,, 800 ,,	+2 + 2	−2 + 4	
,, 900 ,,	+4 + 2	−2 + 10	
,, 1,000 ,,	+4 + 6	+2 + 10	
,, 1,100 ,,		+4 + 10	
,, 1,200 ,,		+6 + 11	

In these four cases collapse was not interfered with by adhesions. If adhesions or pleural effusion reduce the size of the pneumothorax cavity, it will sometimes be found that there is a considerable negative pressure at first, but that it rapidly changes. For instance, in one of my cases in which the pneumothorax cavity was gradually becoming obliterated by the spreading of the pleural adhesions, a negative pressure of $-24-12$ was found, but it became $+20+26$ after 250 c.cm. of air had been introduced.

The following table shows the variation of intra-pleural pressure at the initial operation when there are adhesions:

	Case I.	Case II.	Case III.
Initial pressure	$-4-0$	$-4-0$	$-6-0$
After 50 c.cm. air	$+8+12$		—
,, 150 ,,	—	$+19+23$	—
,, 200 ,,	— -	—	$+2+6$

The following table shows the variation of intra-pleural pressure after the formation of pleural effusion:

	Case I.	Case II.	Case III.
Initial pressure	$-6+4$	$-2+4$	$-3-0$
After 100 c.cm. air	$-1+6$	—	—
,, 200 ,,	$+8+14$	—	—
,, 300 ,,	$+16+22$	—	—
,, 400 ,,	—	$+20+22$	—
,, 500 ,,	—	—	$+10+14$

When liquid is replaced by air the quantity of liquid removed must be greater than that of the air added if the intra-pleural pressure is to be lowered. For instance, in one of my cases the pressure in the air-space above the liquid was $-3+1$, after removing 700 c.cm. of liquid it was $-14-6$, but on adding 700 c.cm. of air it became $+3+8$.

The following cases show the effect of replacing liquid with air on the intra-pleural pressure:

I. Pressure $-2+4$.   After removing 1,650 c.cm. of liquid and introducing 1,100 c.cm. of air the pressure was $-4+2$.

II. Pressure $-8+3$.   1,350 c.cm. liquid were removed and 1,100 c.cm. air introduced, and the pressure was $-8+2$.

III. Pressure $-5-4$.   1,250 c.cm. of liquid were removed and 1,000 c.cm. of air introduced, and the pressure was $-4-2$.

The lung can remain well collapsed with a negative pressure. Indeed, one almost always finds a negative intra-pleural pressure when the patient attends for a refill, yet X-ray shows that the lung is well collapsed and that very little re-expansion has taken place since the last refill. A positive pressure left after a refill is soon converted into a negative one. It is not often that one has the chance of seeing how quickly the intra-pleural pressure alters, because at the initial operation only a small quantity of air is given and the initial pressure is altered very little, whereas in the later stages of the treatment, when there is a positive pressure, the refills are given at long intervals. In the two following cases, however, a large initial quantity of air was given to check haemoptysis, and the pressures were as follows:

I. Initial pressure	$-11-8$
After 1,400 c.cm. of air	$+1+5$
36 hours later	$-11-8$

II. Initial pressure $-10-8$
    After 900 c.cm. of air $-2-0$
    Two days later $-7-5$

In the following three cases there was much adherent pleura:

I. Initial pressure $-9-5$
    After 120 c.cm. of air $+10+14$
    24 hours later $-4+1$

II. Initial pressure $-4-2$
    After 300 c.cm. of air $+1+5$
    16 hours later $-2-0$

III. Initial pressure $-5-2$
    After 500 c.cm. of air $0+3$
    24 hours later $-5-2$

It sometimes happens that after a refill the patient complains of dyspnoea and tightness of the chest, and a needle is put into the pleural cavity to find the pressure and, if necessary, to remove some of the gas.

I. Initial pressure before the fourth refill $-13-9$
    After 700 c.cm. of air $-3+1$
    3 hours later $-5+2$

II. Initial pressure before the fifth refill $-5-1$
    After 700 c.cm. of air $+7+11$
    4 hours later $0+4$

III. Pressure before initial operation $-6-3$
    After 350 c.cm. of air $-4-1$
    16 hours later $-6-4$

These cases do not show any evidence of a temporary increase in the volume of gas after a refill.

If a big positive pressure is reached it will sometimes be found that the oscillations recorded by the manometer are reversed—that is, a higher pressure is recorded with inspiration than with expiration. Bjure (1920) describes three cases in which the pressure was increased during inspiration, but normal fluctuations were recorded when the patient was told to use costal and not abdominal respiration. The reversed fluctuations in such cases are due to the descent of the diaphragm during inspiration on the healthy side and ascent on the other side, and this can be well demonstrated by X-rays.

If the pneumothorax needle is accidentally put into the abdominal cavity the readings on the manometer are reversed, the pressure being higher during inspiration.

H. de Carle Woodcock (1915) at a post-mortem examination found an intra-pleural pressure of -1.5 inches of water. Intestinal pressure was $+2$, but after freely puncturing the intestine and allowing the gas to escape the intra-pleural pressure became -3.5. It would appear, therefore, that distension of the bowels had some effect on intra-pleural pressure. This may account for the curious changes of pressure very occasionally found at refills. For instance, in one of my cases the patient was having 800 c.cm. of air every three weeks, the pressure being taken from about $-8-2$ to $+6+10$. At the 14th refill the pressure was $-2+4$ and 500 c.cm. raised it to $+15+17$. No liquid was seen by X-ray and at subsequent refills the patient was able to take 700–900 c.cm. as previously.

It must be remembered, however, that such changes in pressure are almost invariably due either to the pressure of an effusion or to extension of adhesions diminishing the pneumothorax space. The development of dry pleurisy may cause a high intra-pleural pressure, though no liquid forms. Perforation of the visceral pleura often causes a very high intra-pleural pressure. In one of my cases the pressure after perforation was $+12+29$ and it was reduced to $-1+6$ by removing 1,200 c.cm. of gas.

It has been stated that for a short time after a refill, before the gases in the pleural cavity are balanced by interchange with the gases comprising alveolar air, the actual volume of gas in the pleural cavity is increased (Rist and Strohl, 1920). This would raise the intra-pleural pressure and be one explanation of the dyspnoea not infrequently seen some three or four hours after a refill. It is not my experience, however, to find this rise of pressure.

In one case a patient came to hospital with the right pleural cavity full of liquid, and the mediastinum pushed right over as shown in Plate II. It was thought to be important to know what effect treatment would have on the pressure in the left pleural cavity, and after removing some liquid the following pressures were taken :

Amount of Gas.	On R. Side.	L. (healthy) Side.
0	$-6-4$	$-8-6$
200 c.cm.	$+3+9$	$-8-6$
300 c.cm.	$+4+12$	$-8-6$

Plate III shows the condition some time later, when the liquid had all been removed and replaced by gas, and Plate IV shows the condition a year later, when the mediastinum had returned to its normal position. On another occasion it was found necessary to find the pressure on the other side, and the following pressures were obtained :

Amount of Gas.	L. (operation) Side.	R. (healthy) Side.
0	$-6-2$	$-5-3$
600 c.cm.	$+2+5$	$-5-3$
800 c.cm.	$+6+9$	$-5-3$

It may be concluded, therefore, that in compressing one lung by artificial pneumothorax one does not interfere with the pressure in the opposite pleural cavity, even if the mediastinum is displaced. Of course it is only on the rarest occasions that one has the opportunity of taking pressures on the two sides—for example, when one is contemplating a double artificial pneumothorax.

Altitude also affects the intra-pleural volume. Riviere (1917, p. 80) says that in the case of a full pneumothorax of 3 or 4 litres an altitude of 3,250 to 5,000 ft. is equivalent to an addition of 400-800 c.cm. of gas.

Chapter VII.

The Dangers of inducing Artificial Pneumothorax.

Woodcock (1915) writes : ' There are dangers in connexion with the production of artificial pneumothorax, but the greatest —and about this let there be no mistake—is the neglect in which it is held.'

It is because of these dangers that I wait until other methods of treatment have proved unsatisfactory before advising pneumothorax treatment in an early and good case, unless there are any special indications. It may well be, however, that with increased experience I shall change this opinion. For, although I have occasionally seen cases in which pneumothorax treatment has hastened the end. I have never myself seen such a result except in patients whose lives could not possibly have been prolonged for more than a few months by any other form of treatment. On the other hand, every physician must have seen patients who have had early and thorough sanatorium treatment dying of pulmonary tuberculosis, and it is because of the frequency of such cases that one asks oneself whether artificial pneumothorax should not have been advised in the early stages. Of 200 deaths from this disease amongst Brompton Hospital patients I found that the average duration of life from the first symptom was 26 months. More than 70 per cent. of patients in Groups I and II (Turban, Gerhardt) with tubercle bacilli in the sputum die within four years (Bardswell, 1921). Of course the mortality is much greater if Group III is included. It is a desperate disease, and before rejecting pneumothorax treatment one should weigh the dangers of the disease with the disadvantages of the treatment, which is not as dangerous or heroic as many seem to believe. In this chapter the dangers of the operation itself will be discussed. and in the next the complications which may arise during the treatment.

Pleural Shock.

This is a very serious but rare accident which may occur whenever the pleura is cut or punctured. It may also occur when the pleural cavity is being washed out. Possibly it is caused by afferent impulses to the medulla. In mild cases the symptoms are slight faintness and dizziness only. In worse cases the symptoms are more severe. The patient feels unable to take a breath, the complexion becomes livid, the pulse rapid, irregular. or perhaps imperceptible, and consciousness is lost. Recovery, however, may take place.

Stivelman (1919) describes the case of a patient with pulmonary tuberculosis who had a fibroma removed from his arm under cocaine and adrenalin on 1st February and there was no ill result. On 20th February it was proposed to make an artificial pneumothorax, and after giving an injection of morphia gr. 1/8, the pleura was anaesthetized with 1·5 c.cm. of a 0·75 per cent. solution of cocaine and adrenalin 1 in 8,000, but before the hypodermic needle was

withdrawn the patient collapsed, the pulse was just perceptible, there was photophobia and stertorous breathing and the patient became livid. Stimulants were given and he recovered after an hour and a half. Two days later he had a similar but worse attack whilst the pleura was being anaesthetized. He was completely blind for four hours and photophobia lasted for 24 hours. He was quite well in two days' time.

McKnight, Gammon, and Knowles (1918–19) had a case in which pleural shock occurred at a refill some three months after artificial pneumothorax had been started. The patient suddenly sank back unconscious, with stertorous breathing and tonic contraction of the entire body. After a quarter of an hour the tonic spasm relaxed, he talked wildly and said he could not see. There was complete loss of sight for two days and then gradual recovery.

Saugman (1913) had two cases of sudden death from pleural shock out of 5,000 punctures on 186 patients. Webb, Gilbert, James, and Havens (1914) had no case of pleural shock with 900 injections. Morris (1918–19) out of 202 cases had one case of pleural shock in which the patient became unconscious, but recovered after 20 minutes. Shortle (1918–19) states that he has made over 7,000 punctures and had no case of pleural shock.

Out of 2,332 punctures I have had two cases which may have been pleural shock. In one, after 400 c.cm. of air had been put into the pleural cavity, at the 18th refill the patient complained of a sudden difficulty in breathing and faintness. I withdrew the needle at once and the patient had quite recovered in about two minutes. He never had these sensations at any subsequent or previous refill. A local anaesthetic had been used as usual.

In the second case the patient was a man of 38, very ill with acute tuberculosis which had followed pleurisy. The whole of the left lung was involved. He was given an injection of morphia gr. ¼ half an hour before the operation. The track of the needle and the pleura were anaesthetized with a 2 per cent. solution of novocain and an attempt made to induce a pneumothorax from the left axilla, but it failed. The patient said he felt no pain at all. A second attempt was made at the back after anaesthetizing the pleura as before, but again the pleural cavity could not be found. I was just about to withdraw the needle when the patient suddenly said he could not breathe. I withdrew the needle at once, and the patient sat up, gave a few gasps and died. The needle was cut off from the gas chamber and no air had been allowed to flow. Also there was no movement at all on the manometer, so that even the small quantity of air in the tubing could not have been sucked through the needle. There was no post-mortem examination.

To prevent pleural shock an injection of morphia or omnopon should be given before the first operation. The pleura should be thoroughly anaesthetized with novocain before the initial operation and every refill. It is important to make certain that the novocain actually reaches the pleura. If the patient feels the pneumothorax needle piercing the pleura the local anaesthetic

has not been properly given. It is quite useless to anaesthetize the skin and subcutaneous tissues only. I consider the use of a local anaesthetic a very important part of the operation, but should mention that Stivelman (1919) found pleural shock equally common, whether or not a local anaesthetic had been used, amongst 867 patients treated by 19 American doctors. It has been suggested that there is less chance of pleural shock if the gas is warmed before it enters the pleural cavity. Although pleural shock may occur at any refill it is more common at the initial operation, and, moreover, some patients seem to have a special tendency to pleural shock, which occurs every time the pleura is punctured. For this reason alone I do not agree with those who believe these symptoms are due to gas embolism and are inclined to doubt the existence of pleural shock.

When it does occur, the needle should be withdrawn at once, an injection of pituitary extract or some other stimulant should be given, hot bottles applied to the chest and artificial respiration performed.

If cocaine is used for local anaesthesia it may produce poisoning, and it is possible that some mild cases described as pleural shock may really have been cases of cocaine poisoning.

Gas Embolism.

The very rare cases of sudden death during puncture of the pleura are probably due to pleural shock. No case of gas embolism occurred in my series.

Forlanini found that 6-8 c.cm. N_2 could be put into a dog's left ventricle and 2-3 c.cm. into its carotid artery without ill effect. If gas gets into the systemic veins it has to pass through the pulmonary capillaries. It is, therefore, only the pulmonary veins that are important in the matter of embolism. These contain arterial blood, so that it is not necessary to use oxygen instead of any other gas for the initial operation. The use of carbon dioxide has been suggested as being quickly absorbed by the plasma (Grass, 1921). If the needle enters a large vessel the blood is forced up the needle and can be seen in the glass tube; also the manometer shows a steadily rising positive pressure without oscillations. If an ordinary large blunt Riviere needle is used there can be no danger of entering the smaller vessels. Moreover, when blood enters the needle it quickly clots and blocks the needle. If the needle is in the lung no gas can enter the circulation unless it is under pressure. Stivelman (1919) found no case of gas embolism amongst 867 cases treated by 19 American doctors. He considers it is an accident that need not happen. He thinks that air escaping from ruptured alveoli can rarely cause embolism or it would have been found in some of the many cases of wounds of lung during the war. Webb, Gilbert, James, and Havens (1914) describe a case in which, during a refilling, unconsciousness and stertorous breathing occurred for a few moments and the next day a transient weakness of one hand was noticed.

C

Vere Pearson (1921) said that the only case suggestive of gas embolism he has seen occurred some time ago when sometimes he used to try to separate adherent pleura by high pressures and frequent refills. The patient became semi-conscious for a few moments and afterwards for several hours had partial hemianopia and hemiparesis.

Cetrángolo (1919) describes a case in which the needle was felt to pass the pleura, but no manometer movements were recorded. Oxygen was introduced and the patient at once complained of severe praecordial pain and numbness of one arm. Convulsive movements and unconsciousness followed and the heart and respiration stopped. The patient recovered after artificial respiration and stimulants had been applied, but there was facial paralysis for a few hours. The patient was well the next day.

Rist (1913) says, ' We can repeat with Forlanini that cerebral embolism belongs to the historical period of pneumothorax therapy '.

If gas embolism occurs it would seem probable that gas entered the pulmonary veins and death was due to obstruction of the coronary vessels.

Gas embolism is indeed a very rare accident, and it can be avoided if the following precautions are taken :

1. Allow the gas to be sucked in very cautiously and use no pressure until the movements of the manometer make it certain that the needle is in the pleural cavity.

2. The needle and tubing should at first be connected only with the manometer, being clipped off from the gas chamber.

3. Use a large and blunt needle for the first operation.

4. Give the patient morphia or omnopon before the operation so that he may keep quiet. Coughing or deep breathing should be prevented, at least until the needle is in the pleural cavity and the gas flowing freely.

Puncture of the Lung.

If the visceral and parietal pleura are adherent it often happens that the needle passes straight through into the lung. In this case a negative pressure is usually registered on the manometer, increasing at first with each inspiration, but showing no oscillations. The needle soon becomes blocked with clotted blood. This accident may be followed by slight haemoptysis, but usually there are no ill effects. If the pleura is not adherent it is possible to avoid piercing the visceral pleura by using a blunt Riviere needle for the initial operation and by being gentle. A possible cause of ruptured lung in some cases may be the piercing of a caseous patch of lung by the pneumothorax needle.

Puncture of a Large Vessel or of the Heart.

Vere Pearson (1919) describes a case in which the needle entered the pericardium. The manometer showed negative oscillation synchronous with the heart. The needle was withdrawn and there were no ill effects.

Minor (1917) was inducing a pneumothorax on a young woman with an old fibroid lesion. Suddenly she gasped and turned pale. Blood rushed up the tubing as far as the gas chamber. The needle was at once withdrawn and there were no ill effects.

I have had two similar cases. One a patient who had finished the treatment two years before and in whom I was trying to reproduce a pneumothorax. The other a patient with much fibrosis. In both cases the manometer showed a rapidly increasing positive pressure and blood rushed up the tubing, but there was no pain or discomfort of any sort and no after-effect.

CHAPTER VIII.

COMPLICATIONS.

Pleurisy.

A small lesion of pleurisy frequently leads to the pleural layers becoming adherent and the disease arrested. In cases of pneumothorax this cannot occur, since the visceral and parietal pleura are separated by gas, and consequently pleural effusion is a very common complication. Dry pleurisy may occur as a complication of artificial pneumothorax, and Riviere thinks it is not uncommon at the site of puncture, especially if many punctures have been made at the same place. The symptoms of dry pleurisy are malaise and slight pain or aching in the chest. There is often a little tenderness on palpation over the pleurisy, and the note on percussion is impaired. If a refill is given it is found that less gas than usual is required to reach the former pressure. The treatment of such cases is to keep the patient in bed and apply antiphlogistine to the side. Saugman believes that salicylates have a specific effect in these cases.
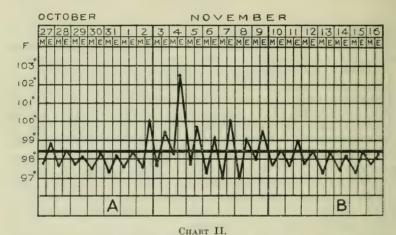
Pleural effusion is the most frequent complication of artificial pneumothorax. There may be no symptoms or the patient may complain of malaise and slight pain. Sometimes there is vomiting and the condition resembles an acute gastric disturbance. There is usually some pyrexia for a few days. Chart II illustrates the onset of pleural effusion. After three or four days the symptoms and pyrexia usually disappear, but occasionally the temperature remains high and the patient's condition becomes steadily worse. In these latter cases it is found that the tuberculosis is spreading in the lungs, and the development of the liquid seems to have been the starting-point of a general break-down. Fortunately such cases are rare. The physical signs of effusion are obvious. Shifting dullness can be demonstrated even if there is only a very small amount of liquid. The level of the liquid is horizontal and there is no parabolic curve. Vocal fremitus is absent over the liquid but present over the air-space above it. Breath sounds are usually absent over both air-space and liquid, but if the lung is not completely collapsed the breath sounds are often better conducted by the liquid, and are bronchial. The succussion

splash is one of the best physical signs and can be heard even in the smallest effusions. The patient will often complain of feeling liquid splashing about in his chest.

X-ray shows the presence of liquid beyond doubt, but the patient must be examined in the upright position. A very small effusion can often be detected only by X-ray examination.

In my series there were 37 cases of effusion, not counting those few resulting from rupture of lung. All these 37 occurred in cases of pulmonary tuberculosis. There was not one case of effusion in the 18 non-tuberculous cases treated by artificial pneumothorax. The longer the treatment the greater is the prevalence of effusion. Thus Saugman found 21 per cent. cases within the first 3 months, 44 per cent. within the first year, and 50 per cent. within 3½ years developed effusion. Weinstein, of Davos, considers the formation of effusion more common in advanced cases. In his series effusion formed in 70 per cent. of

CHART II.

A. 10th refill.   600 c.cm. of air given.
B. 11th refill.   300 c.cm. of air given.

advanced cases, in 33 per cent. of medium cases, and in 10 per cent. of mild cases.

Kendall and Alexander (1918–19) found the complication more common in advanced or acute cases, and also believed that if the intra-pleural pressure was high, or the patient took much exercise, effusion was especially liable to form.

The separation of the visceral and parietal pleura and consequent prevention of adhesions are of great importance in the causation of effusion. Again, the constant irritation of the pleura by gas may have some influence in causing effusion. That the pleura is affected by the gas is shown by the fact that the visceral and parietal layers almost invariably become adherent if allowed to come in contact after pneumothorax. Possibly the collapse of the lung and consequent interference with the escape of lymph from the lung along the subpleural lymphatics and the structures of the hilum may cause effusion.

If precautions are taken during the operation the pleura need never be infected by the needle, but it may become infected by the rare accident, rupture of the lung. Apart from this I think the effusion is almost always an exudate due to tuberculous pleurisy, not only because the tubercle bacillus is the only organism I have found, but also because effusion has not formed in my non-tuberculous cases.

In one of my cases the patient was doing well, had lost tubercle bacilli from the sputum, and was at work. After 20 months of treatment he suddenly developed pain in the chest and dyspnoea. There was considerable pyrexia and liquid was found in the pleural cavity. The liquid was much blood-stained. Two months later the patient died, and he was found to have an extensive and recent tuberculous pleurisy and pericarditis.

In the majority of cases the liquid is amber coloured at first, but later becomes ordinary green tuberculous pus. In the early stages tubercle bacilli were not commonly found in my series, but they were present in all cases in the later stages. No other organism was ever found.

The clear amber liquid of the early stages has a specific gravity of 1020–6 and contains albumin. There are very few cells, but of the cells 80 to 90 per cent. are lymphocytes. About 8 per cent. are polymorphonuclear leucocytes, and there are usually about 5 per cent. endothelial cells. Occasionally eosinophiles are found.

The Effects of Pleural Effusion.

Professor Saugman (1920) gives the following table :—

	With effusion.		Without effusion.	
January 1919.	No.	Per Cent.	No.	Per Cent.
Able to work	31	37·3	24	40
Unable to work	4	4·8	1	1·6
Dead	48	57·8	32	53·3
Ill or dead from other causes			3	5

From this it would seem that cases without pleural effusion do slightly better than those with it. It must be remembered, however, that effusion is most likely to form in the acute and serious cases, so that its presence in the chronic or mild cases usually need not be regarded as a serious complication. Jacot (1915) in an exhaustive study of purulent effusion in artificial pneumothorax recognizes four types of cases. In one (36 per cent. of his cases) the serous liquid develops into tuberculous pus, which he recommends should be removed from time to time. The patient's condition remains good. In the second (16 per cent.) after a period of well-being the patient's condition suddenly becomes grave, there is a hectic temperature, and the pulmonary tuberculosis spreads rapidly to a fatal issue. In the third (28 per cent.) the purulent effusion begins with pyrexia and the patient's condition is bad, but eventually the condition settles down and becomes as in the first type. In the fourth group (20 per cent.) the condition is due to rupture of the lung. These cases were all fatal.

In my series of 37 the cases seemed to divide themselves into three groups, and as I do not include cases due to rupture of the lung this seems to agree closely with Jacot. 1. Development of small effusions with or without slight malaise and pyrexia. The presence of liquid was confirmed by X-ray examination. The liquid was quickly absorbed without any being withdrawn. 2. The development of liquid which increased in quantity and showed no signs of being absorbed. It either remained serous or became tuberculous pus. 3. The development of liquid with pyrexia and serious constitutional symptoms, associated with a rapid increase in the pulmonary lesions and leading to a fatal issue.

Pyopneumothorax resulting from rupture of lung I consider a separate condition altogether.

One result of pleural effusion is that the pleura becomes much thickened and it may be that the lung becomes so encapsulated that it is unable to re-expand. Again, the contractions of adhesions may cause a gradual obliteration of the pleural cavity. I have found this last result often leads to the formation of considerable fibrosis and may actually be beneficial.

Treatment of Pleural Effusion.

In the mild cases the patient should be kept in bed during the initial stage of malaise, and the treatment is the same as for dry pleurisy. When a large effusion forms, treatment depends upon the condition of the patient.

In the acute cases when there is a purulent effusion it should be aspirated and replaced with air or oxygen. If the pus re-forms the pleural cavity should be washed out with normal saline solution or some weak antiseptic. Collargol has been recommended. Dakin's solution is very good, but should not be used if there is a communication between the lung and pleural cavity, as it is irritating to the bronchial mucous membrane. I have used hypertonic saline solution, but with no different result from normal saline.

Oxygen is quickly absorbed and the patient must be kept under very careful observation, for the lung must not be allowed to re-expand so that the visceral and parietal layers of pleural come in contact. In these acute cases the pus rapidly re-forms, so that the operation has to be repeated.

In cases where there is a larger effusion, but the condition of the patient remains good, some physicians leave the liquid in the pleural cavity. There are three dangers in this course: one is that in the late stages of treatment the tuberculous pus may break through into the lung. This occurred in one of my cases, and Dr. Vere Pearson describes two such cases (1919). Another is that great thickening of the pleura may develop and so prevent the lung from ever re-expanding. The third is that the pneumothorax cavity may become obliterated by the contraction of adhesions. If, however, an air-space is left above the liquid and the pressure taken from time to time keeps constant,

and if the patient is frequently examined under X-ray, the danger of the pneumothorax cavity becoming obliterated can be no greater than if the liquid is repeatedly withdrawn. The thickening of the pleura would occur whether or not the liquid was removed. In most of my cases when the liquid was removed, it re-formed, so that the operation had to be repeated, often many times.

Auto-serotherapy has been suggested ; that is, the subcutaneous injection of 1 c.cm. of the exudate directly it has been aspirated. This seems dangerous, as the exudate often contains virulent tubercle bacilli.

If the liquid reaccumulates, 10 c.cm. of 2 per cent. formalin in glycerin may be injected into the pleural cavity after the next gas replacement, but it is doubtful whether this has any effect on the formation of the effusion. In one case, where the liquid had been removed four times, I washed out the pleural cavity at the next refill with 2 litres of normal saline and injected 10 c.cm. of 2 per cent. formalin in glycerin, leaving the lung compressed with oxygen. The liquid did not re-form.

Except in a few cases of small effusions, when liquid forms it has to be removed sooner or later. If it is still present after three months it is best to remove it and replace with air or oxygen. That liquid may remain in the pleural cavity for a long time without harm is shown by a case where it developed in February 1919, after pneumothorax had been started in August 1918. The patient kept at work and apparently well until June 1920, when he reported to the hospital. His general condition was excellent, but the R. pleural cavity was full of liquid and the mediastinum much displaced. Between June 1920 and May 1921, $9\frac{1}{2}$ litres of greenish liquid were removed. The Plates II, III, IV show his condition before and after the liquid had been removed. Such a condition should not, of course, have been allowed to arise. I do not. agree with those who, unless the patient becomes distressed, leave effusions indefinitely.

Peters (1921) and Minor (1917) think liquid should be removed only to relieve pressure symptoms. Peters says that the average patient with sterile pus recovers as quickly and as easily as the average patient with only a serofibrinous effusion. This is not my experience, although I agree that cases with sterile purulent effusions often do very well.

Thickened Pleura.

This may occur when there is no effusion, but it is especially frequent in cases of long-standing purulent effusion.

There may be some local thickening of the pleura at the site of the punctures, if many have been made in the same place, but there is also occasionally a general thickening of the pleura. The collapsed lung is at times so bound by the pleura that re-expansion is impossible, but usually re-expansion takes place, even after many years of treatment.

When the visceral and parietal layers of pleura become adherent they are usually much thickened, and if during

pneumothorax treatment the layers of pleura are allowed to come into contact, adhesion almost invariably takes place. In one case, in which a pneumothorax had been produced by the surgical or open method, no refill was given for eight days, and it was then found that the two layers of pleura were firmly adherent.

I have succeeded in reproducing a pneumothorax in one case seven months after the last refill, and obtained quite satisfactory collapse, but the pneumothorax cavity gradually became smaller and smaller, and the treatment had to be stopped after six months because the air-space was obliterated. In two cases I failed to reproduce any pneumothorax at all—one 20 months and the other 12 months after artificial pneumothorax treatment had been stopped. Vere Pearson (1919), however, succeeded in reproducing a pneumothorax in one case, two years after the last refill.

It may be taken, however, that the pleural surfaces will almost certainly become adherent if allowed to come into contact, and therefore that it will not be possible to restart the treatment. This is of great importance when one has to consider how long the treatment should be continued.

Perforation of the Visceral Pleura.

It sometimes happens that a rupture or tear of the visceral pleura occurs and leads to a communication between the lung and the pneumothorax cavity. This is a most serious complication which usually causes fatal empyema. As the lung is already collapsed when the accident happens the perforation does not tend to heal by collapse of the lung, as is the case in ordinary spontaneous pneumothorax.

The symptoms are sudden pain in the chest accompanied by a rise in temperature, which becomes hectic. The patient is acutely ill and liquid soon forms in the pleural cavity and becomes purulent. Occasionally the breath sounds become amphoric over the pneumothorax cavity. The intra-pleural pressure may be much increased if the perforation is valvular, and the patient will become very dyspnoeic until some gas is removed. When there is a free communication between the lung and pleural cavity the percentage of oxygen in the gas is said to be increased (Riviere, 1917, p. 163).

Of Forlanini's 139 cases, rupture of lung occurred in 8, and all died. Burland (1921) describes 9 cases. Of these 3 died within the first month, and 4 in from three to six months.

Hudson (1921) describes the case of a man of 21 who did very well after pneumothorax treatment for five months, when he caught influenza. During a violent fit of coughing he had sudden pain and collapsed. The temperature rose to 105°, and after a day or so effusion formed. Pus was aspirated about every ten days and the cavity washed out with weak lysoform. Three months later rib resection was done and the patient improved; he was alive a year after the perforation, but still had an open empyema wound with tubercle bacilli in the discharge, and he had an

evening temperature of 100°. Powell and Hartley (1921, p. 724) give a detailed description of a case of ruptured pleura.

It has occurred in four of my cases. Two of these were cases of advanced pulmonary tuberculosis with adhesions preventing the complete collapse of lung, and in these death soon followed the rupture of lung.

In one other case the patient, a man of 51, had a severe cough, copious offensive sputum, but containing no tubercle bacilli, two attacks of haemoptysis and physical signs of disease in the left apex and axilla following a left-sided dry pleurisy six months previously. He had been under pneumothorax treatment for three months when suddenly, on 9th October 1921, he had violent pain in the left side and increasing dyspnoea. Four days later he came to the hospital and was readmitted. He was very dyspnoeic and collapsed and the intra-pleural pressure was $+12 +29$. 1,200 c.cm. of gas were removed and the pressure reduced to $-1+6$, after which he was much more comfortable. Two days later foetid pus was aspirated from the pleural cavity, which was then washed out with saline. This was repeated the next day and the patient's condition improved considerably. On 21st October a portion of rib was resected and the pleural cavity drained. On 30th December the patient was up and about, and the wound had healed, except for a small sinus. He had a slight cough and a little expectoration, but otherwise was free from symptoms.

The fourth case was a man of 40. In May he had an operation for nasal polypi, and this was followed by cough and gradually increasing offensive sputum. On 6th October a right artificial pneumothorax was induced, 300 c.cm. of air being given and the end pressure $-5-0$. At that time he had signs of an abscess at the base of the right lung, copious offensive sputum, but free from tubercle bacilli, and he had been having a temperature of $101-102 \cdot 6°$ F. for many weeks. The next day 500 c.cm. of air were given and the pressure taken to $-4+3$. On 10th October the abscess burst into the pneumothorax cavity. The patient was much collapsed and appeared to be *in extremis*. A large quantity of very offensive brown pus was aspirated and the pleural cavity washed out until clear. This was repeated daily until 19th October, when the patient's general condition had improved and a portion of rib was resected and the pleural cavity drained. The patient gradually improved and eventually made a good recovery.

The perforation is apt to take place at the junction of an adhesion and the pleura. Here the pleura is stretched and may tear if there is violent exertion or much coughing. Perforation may also occur as a result of the rupture through the pleura of a caseous lesion in the lungs. Also it might be produced at the initial operation by a caseous lesion being penetrated by the needle.

The treatment of these cases is to aspirate the pus, wash out the pleural cavity and replace with air or oxygen; Dakin's solution should be avoided as the chlorine is very irritating to

the bronchial tubes. Collargol, lysoform, or weak acriflavine may be used. Usually the patient is very acutely ill and the fatal issue cannot be long delayed. If improvement occurs but the pus keeps re-forming, thoracoplasty may be recommended and in certain cases yields satisfactory results.

In patients with complete collapse there is little danger of perforation, but if there are adhesions, and especially if there is lung tissue in the adhesions, the possibility of perforation must always be considered; in such cases high pressures should be avoided and the patients should be strongly warned against taking any sudden exertion.

Pain.

The operation itself should be quite painless. Patients are usually apprehensive, but on finding that they feel nothing except the initial prick of the hypodermic needle they do not dread the refills. Even children become quite used to the treatment and do not dread a refill as a rule. Some people are more sensitive than others, and some patients, especially those who are very ill, always dread a refill. One man described the operation and each refill as agony. He clenched his fists, and beads of perspiration came on his forehead, although he was always given $\frac{1}{4}$ gr. of morphia before treatment. To avoid pain during the operation the track of the needle should be well anaesthetized, the skin stretched and the pneumothorax needle pushed quickly into the pleural cavity. It is not uncommon for patients to complain of pain after the operation or refills. This pain may be severe and last for a few days or it may be a mere feeling of pressure or tightness. It is usually due to stretching of adhesions, but the feeling of tightness may possibly be caused by the interchange of gases causing a temporary increase in the volume of the intra-pleural gas and consequent increase in pressure; or to an increase in pressure owing to a rise in temperature increasing the volume of gas.

One may recognize three types of pain following artificial pneumothorax or refills:

1. The patient first complains of tightness and then actual pain which lasts for a few hours after the refill. It occurs only in patients with adhesions and a high intra-pleural pressure. Doubtless the pain would be more severe and last longer if the pressure were increased, but I always avoid too high a pressure, and abandon the treatment rather than try to break away adhesions by high pressures.

2. A pain which comes on some hours after the refill and is increased by cough or deep breathing. This is often referred to the shoulder and usually to where X-ray proves the presence of adhesions. It is relieved by morphia and does not recur until the next refill. Dr. Morriston Davies tells me that he finds Amidopyrin (gr. vii) and Pot. Brom. (gr. x) almost a specific, and that he never has to give morphia.

3. The sudden snapping of an adhesion. This occurred only once in my series. The patient was a man who had been under

treatment for eight months. He was doing very well, was not at all nervous, and had never complained of pain before, but during one refill he suddenly complained of a sharp pain after about 500 c.cm. of air had been introduced. It lasted for only a second or so and it was possible to finish the refill. He said it was similar to the pain felt when the dentist touches a nerve. There was no effect on the intra-pleural pressure and he had no further pain at any subsequent refill. Dr. de Carle Woodcock tells me that in one of his cases the adhesion was heard to snap by the patient and nurse as well as by himself.

In three of my cases in which the patients felt something give inside them, probably some adherent pleura had been separated, but there was no actual pain. Indeed, in one of these cases the patient had a feeling of tightness and pain, which was relieved at once after the sensation of something giving way in her chest.

In two cases in which only a partial pneumothorax could be induced owing to adherent pleura the patients complained of pain for a day or so before the refills, and this was probably due to pleurisy. the pain being caused by the separated visceral and parietal pleura coming together. In such cases the refills should be given at shorter intervals. In my other cases in which the pneumothorax cavity has gradually become obliterated there has been no pain.

Pain may be due to deep emphysema and is then felt under the sternum and in the throat. It comes on a few hours after the refill, and is accompanied by a sensation of choking and severe dyspnoea. These symptoms last for about six hours, and there are usually no other ill effects.

One patient, who had acute tuberculosis with a very high temperature, complained of a sudden severe pain in the chest two days after the second refill, at which the intra-pleural pressure had been left at $-1-6$. She died the next day and there was no post-mortem examination, but it seems that in this case there had been a perforation of the lung.

Another patient who had been doing well had a sudden sharp pain in the chest. The temperature rose and he became very breathless. Two days later he came to the hospital, and it was found that the intra-pleural pressure, which had been $+8+10$ at the last refill, was $+12+29$. In this case also the visceral pleura had perforated.

Surgical Emphysema.

Superficial emphysema is not uncommon. It occurs especially in patients with a thin chest wall, and if there is a high intra-pleural pressure. By drawing the skin down so that after the operation the puncture in the skin is not just opposite that in the deeper tissues emphysema may be prevented. It is, however, quite a harmless complication and quickly clears up. I have never heard a patient complain of pain from this cause.

Deep emphysema is caused by the air entering a false passage between the pleura layers. It travels to the neck along the trachea and oesophagus and is accompanied by pain and severe

dyspnoea. There may also be difficulty in swallowing and a sensation of choking. These symptoms may be very alarming, but they quickly subside. Hot applications should be applied to the chest and neck, and if the symptoms are severe an injection of morphia may be given.

Infection of the Track of the Needle.

This must be mentioned, but should not occur if aseptic precautions are taken.

Dyspnoea.

There is always a certain amount of dyspnoea, especially in the early stages of the treatment. In the later stages there is often dyspnoea when the lung begins to re-expand (Morriston Davies, 1919, p. 174).

Sometimes after the operation or first few refills the patient complains of severe dyspnoea and may be in serious distress. This usually comes on in the evening and may increase in severity until the patient is gasping for breath. The symptoms are largely nervous and are relieved at once by an injection of morphia. In one of my cases such alarming dyspnoea occurred in the evening after each refill that the treatment had to be abandoned.

The dyspnoea which comes on some three hours after the refill may be due to the temporary increase of gas in the pleural cavity before the balance is established between the alveolar air and the gas in the pleural cavity (Rist and Strohl, 1920). But I can find no evidence of this being so. A rise of temperature might produce an increase of intra-pleural pressure, but in cases of dyspnoea when I have tested the pressure I have invariably found it lower than it was immediately after the refill.

Reaction.

In a case of spontaneous pneumothorax there is almost invariably a febrile reaction. After the initial operation for artificial pneumothorax or after a refill there is occasionally a reaction.
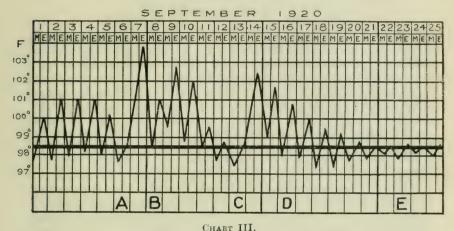
Of 196 cases in which I have induced a pneumothorax there has been a definite reaction in 15. Of these one was a patient with haemoptysis, for which I gave a large initial dose. The reaction had no ill effect and the patient is now keeping very fit: see Chart I, p. 21. In the other cases the doses were small. In my experience, if a patient has a reaction after the initial operation he is liable to reactions after refills, but that after three or four refills the reaction does not recur. Charts III and IV illustrate reactions to the treatment.

Recently Morriston Davies (1921) has drawn attention to the reactions in pneumothorax treatment due to other organisms than the tubercle bacillus. He emphasizes the importance of intestinal stasis.

Displacement of the Mediastinum.

It often happens that during treatment the mediastinum becomes displaced to the healthy side; sometimes this displacement is small, sometimes considerable. The intra-pleural pressure

CHART III.

A. Initial operation.   D. 3rd refill.
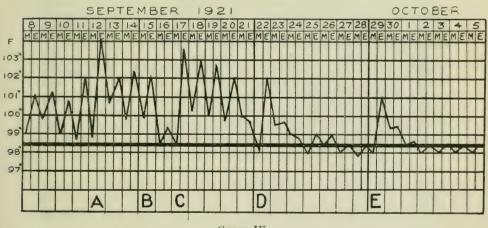B. 1st refill.   E. 4th ,,
C. 2nd ,,

CHART IV.

A. Initial operation.   400 c.cm.   D. 3rd refill.   600 c.cm.
B. 1st refill.   550   ,,   E. 4th ,,   700 ,,
C. 2nd ,,   600   ,,

need not necessarily be high; indeed, it is often negative in spite of considerable displacement.

In such cases I have found that the general well-being of the patient is impaired, and there is usually loss of weight. The intervals between refills should be lengthened and the amount of

gas given diminished, the patient being examined at least twice a week by X-ray. It will be found that as the mediastinum returns to its normal position the condition of the patient improves, and he gains weight. In cases of steady loss of weight displacement of the mediastinum should always be suspected.

General Conditions.

Two of my patients suffered from asthma. Both were cases of bronchiectasis. One, a male, had a very severe attack after about six weeks' pneumothorax treatment, but since then his attacks are less frequent and, he thinks, less severe than before the treatment was started. The other patient suffered from asthma when a child, but had had no attack for several years until the pneumothorax treatment was started in Vienna. The asthma then returned and several attacks were very severe. When the patient came home to London she was free from asthma and refills were given there. However, during a holiday in Yorkshire between the refills she had a bad attack and had to return to London.

The general condition and resistance of patients are good as a rule. I know of one who developed acute appendicitis, had appendicostomy under a general anaesthetic, and made a perfect recovery. One of my patients went through a confinement without trouble. Stater (1918–19) described a patient who, after 15 months' artificial pneumothorax treatment, had a three-months' abortion, and was confined about 18 months later without ill effects. The treatment was kept up and the patient remains fit four years after the treatment was started. Three of Saugman's (1920) patients were confined without relapse during artificial pneumothorax treatment and one of them twice.

Pneumonia occurring in the other lung is a very serious complication, and for this reason one may hesitate to maintain an artificial pneumothorax for too long. Saugman describes the case of a patient who had been treated for six years and then died of pneumonia of the good lung. Post-mortem examination showed complete healing of the lung, and a compressed cavity. Inoculation of a guinea-pig did not produce tuberculosis.

Chapter IX.

Artificial Pneumothorax induced on both sides of the Chest.

Cases in which it is necessary to make a pneumothorax on both sides usually do badly. But it is often possible to transform a rapidly spreading tuberculous lesion into a chronic fibroid lesion by a pneumothorax of quite a short duration. If both right and left lungs are infected it may be possible to check the progress of the disease by inducing a pneumothorax first on one side and then on the other.

Parry Morgan (1917) believes that great advantages may be obtained by partial collapse of first one lung and then the other.

Feldmann of Florence (1920) had a patient who had a right artificial pneumothorax for seven months. Then signs of active disease appeared at the left apex ; so the treatment was stopped for six weeks, when a left pneumothorax was induced, and kept up for 11 months. A year after the completion of the treatment the patient was keeping fit, without apparent active disease.

Forlanini (1911) had two cases. One improved and the improvement was maintained for a year, when he lost sight of the patient. The other improved, but died of influenzal pneumonia.

Burnand (1920) induced a right artificial pneumothorax in June 1915. In October the patient had lost the tubercle bacilli from t'.e sputum and was free from symptoms. In April 1918 the patient had influenza followed by haemoptysis, and pyrexia. In July the patient had tuberculous laryngitis; signs of active disease appeared at the left apex, and tubercle bacilli were present in the sputum. The pneumothorax treatment was stopped and the right lung re-expanded. In January 1919 a left artificial pneumothorax was induced carefully, a negative pressure being left after each refill. The patient was very dyspnoeic, but was able to get up and walk about quietly. He died suddenly in May 1919.

Burnand's second case was a patient for whom a left artificial pneumothorax was induced in January 1918. The patient improved at once, but the symptoms returned in October, and signs of active disease on the right side were found. The treatment was stopped, and the right lung became gradually worse until June 1920, when a right pneumothorax was induced. The dosage varied from 200 to 500 c.cm., and the intervals between each injection were about eight days. A negative pressure was left after each refill. Sixteen refills were given. There was some improvement, but at the end of September right pleural effusion developed, and there was much dyspnoea. The heart became very weak, and the treatment was discontinued.

In one of my patients there were extensive signs of active disease over the left lung, and over the right lung as far as the third rib in the mid clavicular line in front, and the angle of the scapula behind. She had just returned from a sanatorium, where she had become much worse, the physical signs having extended very rapidly. A left pneumothorax was induced, and four refills were given. The treatment was then stopped for seven weeks, when a right pneumothorax was made and five refills given. The patient was very dyspnoeic, but there was less sputum, and the cough was not so troublesome. She was able to get up for four hours daily, but no further improvement occurred.

Saugman (1921) describes seven cases in which he made a bilateral pneumothorax. One had the left lung collapsed from November 1912 to July 1913, and the right lung from January 1914 to June 1915. Since then he has been in good health, and was known to be still at work in 1919. All the other six cases died.

There can be no doubt that artificial pneumothorax is much more likely to be successful in unilateral cases, but if the other lung is involved or becomes involved during treatment, it may

be possible to arrest the disease or, at least, convert it into a slowly progressing fibroid lesion by a double pneumothorax. The chief complaint in such cases is dyspnoea, and I think the vital capacity percentage taken by Dreyer's (1920) method useful in such cases. If the vital capacity does not improve considerably as the lung is allowed to re-expand, the patient will not be able to stand a pneumothorax on the other side.

Chapter X.

The Effect of Artificial Pneumothorax on the Lungs, other Organs, and on Vital Capacity.

During normal inspiration the lung does not expand uniformly or equally in all directions. The larger infundibula which are situated just beneath the pleura are the most expansile, and the part of the lung around the root is the least expansile (Keith, 1909). When the normal lung collapses it is the subpleural zone which first yields, and the whole lung collapses into a ball-shaped mass around the root. Plate V shows this condition. In disease the collapse is affected by the disease itself, and by adhesions which may hold the lung to the chest wall in places. Plate VI shows the lung collapsed along the mediastinum with an apical adhesion. Plate VII shows incomplete collapse owing to adhesions. A lung may be collapsed for years and yet re-expand when the air in the pneumothorax cavity is allowed to become absorbed. In some cases, however, the visceral pleura becomes so much thickened that re-expansion is impossible.

The following case illustrates the condition of the lung after a long period of collapse. The patient, a man of 42, developed tuberculosis of the right lung in March 1918. He had a large haemoptysis in April, and several other attacks until March 1919, when artificial pneumothorax was induced. At this time there were signs of infiltration of all three lobes of the right lung. Tubercle bacilli were present, there was evening pyrexia, and the patient's weight was 10 st. 4½ lb. His condition soon improved, and he lost the tubercle bacilli from the sputum. In May 1921 his weight was 11 st., and his condition was considered satisfactory. He had a slight dry cough, but no sputum, and the pneumothorax treatment was being continued. On 25th May he was suddenly taken ill with pericardial pain and dyspnoea, and, becoming gradually worse, died on 25th July, some two years and four months after the onset of the treatment.

Post mortem both parietal and visceral layers of the pericardium were much thickened, and microscopically showed fibrosis, and tubercle bacilli were present. There was no pericardial effusion. The right parietal pleura was much thickened and firmly adherent to the thoracic wall and diaphragm. On its inner surface were large flakes of lymph and hard cartilaginous plaques, some being an inch in diameter. The visceral layer was similar and bound the lung so firmly that re-expansion would not have been possible.

There were no adhesions between the visceral and parietal layers. Microscopically the pleura showed much fibrosis and tubercle bacilli were present. In the right pleural cavity was much blood-stained liquid. The right lung was completely collapsed, tough to cut, and scattered throughout were several small calcareous deposits. Microscopically were seen several caseous patches completely cut off by fibrous tissue which surrounded them. No giant cells and no tubercle bacilli were seen. There were some young fibroblasts amongst the alveoli, but there was no general fibrosis. There was no brown induration, or signs of congestion of the lung. The left lung and pleura showed no signs of tuber-culosis old or new, and microscopically there was no sign of congestion of the lung. The bronchial glands were enlarged, the cervical and abdominal glands normal. The liver was displaced downwards and the right side of the diaphragm was convex towards the abdomen. This case is interesting in showing the absence of any massive fibrosis of the diseased lung after over two years' collapse. At the same time there was no sign of active disease of lung, the caseous patches being completely encircled by fibrous tissue. It should also be noted that there were no signs to indicate that there had been any congestion of either lung.

The effect of pneumothorax on the circulation in the lungs has been much discussed. The intra-pleural pressure is very rarely raised above a pressure of 20 cm. of water, and this should not affect the circulation. During pneumothorax treatment one almost always finds a negative pressure when starting a refill. X-ray shows that a healthy lung is less translucent after the other lung has been collapsed than it was before, and this increased opacity is said to be due to the hyperaemia. Further, it has frequently been noticed that a small lesion in the better lung disappears or becomes much improved when the other lung has been collapsed, and this has been ascribed to hyperaemia. One must remember, however, that in tuberculosis, removal or treat-ment of the main lesion is often beneficial to other lesions. For instance, tuberculosis of the larynx is improved by pneumothorax, and tuberculosis of the bladder by excision of the diseased kidney.

In recent experiments Corper and Rensch (1920–1) injected suspensions of Prussian blue and scarlet red intravenously into rabbits. If the injection was made half an hour after artificial pneumothorax the suspensions were found uniformly distributed over the two lungs, and the Prussian blue gradually disappeared uniformly on the two sides within the next few hours. When the pneumothorax had been maintained for two weeks before injection the same result was noted, but in an average over a series of rabbits where the pneumothorax had been maintained for four weeks before the intravenous injection there was found to be slightly less pigment in the compressed than in the uncompressed lung, though the difference was not sufficient to be detected microscopically.

The blood pressure is found to be unaltered after artificial pneumothorax. The pulse rate is usually slightly quicker after the treatment, but rapidly falls to the usual rate.

50

The heart, with the mediastinum, is drawn over to the healthy side, but the heart itself is not affected even when the treatment has been kept up for many years. The diaphragm is depressed, and if the intra-pleural pressure is high, may actually be inverted. Seen with the X-ray, it will be observed that if the intra-pleural pressure is positive, there may be a see-saw movement of the diaphragm, that part on the pneumothorax side moving upwards with inspiration and downwards with expiration. This is known as Kienbock's phenomenon. The flaccid part of the diaphragm being thus pushed up into the thorax by increased abdominal pressure loses its piston action. In most of my cases even with a high intra-pleural pressure Kienbock's phenomenon was not present.

I have not noticed severe visceroptosis caused by pneumothorax treatment, but cases of visceroptosis do very badly, and I consider this affection to be one of the most important contra-indications to the treatment (Keith, 1903).

The general health of the patient is usually improved at once by pneumothorax treatment. There often is, however, a loss of weight. This usually occurs when the mediastinum is much displaced, and it can be remedied in most cases by altering the intervals between refills and finding the optimum pressure for the individual patient.

The Effect of Artificial Pneumothorax on Vital Capacity.

Case I. Male, 28. Onset of pulmonary tuberculosis March 1919. Sanatorium treatment July–December, 1919. March 1920 tubercle bacilli present. Signs of active disease at the apices of the upper and lower lobes on the left side. Vital capacity 2570 c.cm.[1] Percentage −41.
July. V. C. 2450 c.cm. Percentage −44.
23rd August. V. C. 2250 c.cm. Percentage −48·5.
27th August. Artificial pneumothorax. 900 c.cm. of air introduced, the end pressure −1. An hour later:
  V. C. 1560 c.cm. Percentage −65.
30th August. Before the first refill. Pressure −6·5.
  V. C. 2050 c.cm. Percentage −53.
  One hour after refill of 900 c.cm. of air and pressure −2.
  V. C. 1680 c.cm. Percentage −61·6.
2nd September. Before the second refill. Pressure −5.
  V. C. 1900 c.cm. Percentage −56·5.
  One hour after refill of 800 c.cm. and pressure 0.
  V. C. 1400 c.cm. Percentage −68.

This case illustrates the effect of large initial doses. The patient's vital capacity was getting gradually worse before treatment. 900 c.cm. of air reduced the vital capacity by 690 c.cm. Three days later the vital capacity increased 490 c.cm. and fell 370 c.cm. on the addition of 900 c.cm. of air into the pleural cavity. Three days later it rose 220 c.cm. and was reduced 500 c.cm. by a refill of 800 c.cm.

Case II. The following case illustrates the effect of the initial doses. Male, aged 19. Two years' history of pulmonary tuberculosis. Signs of extensive disease of the right lung. Tubercle bacilli present.

[1] These percentages below normal are worked out according to Dreyer's (1920) tables.

2nd September.   Before artificial pneumothorax.
    V. C. 2380.   Percentage −45·3.
3rd September.   Twelve hours after 700 c.cm. of air had been introduced.   End
        pressure −2·5.
    V. C. 1800.   Percentage 58·7.
6th September.   Seventy-two hours after the first refill.   Pressure −4.
    V. C. 2450.   Percentage −43·6.
    Two hours after 600 c.cm. of air had been introduced.   Pressure −0·5.
    V. C. 1700.   Percentage −60·8.
8th September.   Forty-eight hours since the second refill.
    V. C. 2050.   Percentage −53.
9th September.   Two hours after the third refill of 900 c.cm.   Pressure 0.
    V. C. 1500.   Percentage −65·5.

Case III.   Male, aged 23.   After one year's pneumothorax treatment for
pulmonary tuberculosis, and 4 weeks since the last refill.   Intra-pleural
pressure −6.
    V. C. 2180.   Percentage −52.
    One hour after a refill of 1200 c.cm.   Pressure +8.
    V. C. 1700.   Percentage −62·8.
    Again 4 weeks since last refill.   Pressure −5.
    V. C. 2440.   Percentage −46·5.
    One hour after a refill of 1500 c.cm.   Pressure +9.
    V. C. 1570.   Percentage −65·6.
    Again 4 weeks since last refill.   Pressure −1.
    V. C. 2100.   Percentage −54.
    One hour after a refill of 800 c.cm.   Pressure +8
    V. C. 1680.   Percentage −63·2.
    Again 4 weeks since last refill.   Pressure −4·5.
    V. C. 2410.   Percentage −47.
    One hour after a refill of 1300 c.cm.   Pressure +5.
    V. C. 1720.   Percentage −63.
    Again 4 weeks since last refill.   Pressure −4.
    V. C. 2310.   Percentage −49·4.
    One hour after a refill of 1300 c.cm.   Pressure +4·5.
    V. C. 1650.   Percentage −64.

From this it would appear that an intra-pleural pressure of
−4·5 is the optimum pressure.   Pressures of −6 and −1 give
a worse vital capacity.

Case IV.   The following two cases illustrate the re-expansion of lung.
Male, aged 51.   After over two years of pneumothorax treatment for pulmonary
tuberculosis.
    Before a refill.
    V. C. 1870.   Percentage −46·7.
    Three months after completion of treatment.
    V. C. 2480.   Percentage −29·1.

Case V.   Male, aged 31.   After two years pneumothorax treatment for
pulmonary tuberculosis and six weeks since the last refill.   Intra-pleural
pressure −8.
    V. C. 3070   Percentage −49·9.
    One hour after refill of 1100 c.cm.   Pressure +7.
    V. C. 2550.   Percentage −55·5.
    Again six weeks since last refill.   Pressure −8.
    V. C. 3220.   Percentage −44·6.
    One hour after refill of 1100 c.cm.   Pressure +10.
    V. C. 2690.   Percentage −53·5.
    Five months after completion of treatment.
    V. C. 3490.   Percentage −39·5.
    Eight months after completion of treatment.
    V. C. 3780.   Percentage −34·5.

Case VI. Male, aged 30. Infiltration of the upper and lower apices of the left lung. Tubercle bacilli present.

> Before pneumothorax treatment was started.
>   V. C. 2660. Percentage −22·2.
> After a year's treatment. Intra-pleural pressure −17.
>   V. C. 2200. Percentage −35·6.
> An hour after removing 500 c.cm. of liquid and introducing 1000 c.cm. of air. Pressure +13.
>   V. C. 2080. Percentage −39.
> Six weeks later. Pressure −16.
>   V. C. 2360. Percentage −31.
> An hour after a refill of 500 c.cm. of air. Pressure +18.
>   V. C. 2210. Percentage −35·5.

Here great changes in pressure cause a very slight alteration in the vital capacity, probably because the lung was fully collapsed by the liquid.

Chapter XI.

The Value of X-ray.

In pneumothorax treatment I consider the use of X-ray to be essential. In the first place it is useful to have a skiagram of the chest before beginning the treatment. Not only does this help the clinical examination as to the condition of both lungs, but it frequently gives assistance as to the presence and position of cavities and adhesions and thus helps one to decide the site at which to puncture the pleura. The chest should always be examined with the screen and the position of the heart and movements of the lungs and diaphragm noted. Plate VIII shows the condition of a chest before treatment. Plate IX is the same chest three weeks later. It will be seen that the lung is collapsing well, but with a few adhesions. It may also be noted that the right or better lung is less translucent in the second plate, and this has been ascribed to hyperaemia.

Plate X shows a chest in the early stages of treatment. It will be seen that the lung is collapsing well and is free from adhesions. It is only by the X-ray that one can learn the exact amount and direction of the collapse of lung. One often sees that a portion of the lung remains uncollapsed, but by increasing the pressure at the next refill it is collapsed, and symptoms may be relieved in consequence. One can also note the rate at which the lung re-expands between the refills, and the direction in which that re-expansion takes place. This is of the greatest value, taken in conjunction with the symptoms, for estimating the correct interval that should be left between refills.

Plate XI shows complete collapse of lung in a patient who had been under treatment for over two years. The skiagram was taken just after a refill. No further refills were given, and Plates XII and XIII show the same chest six and eight weeks later. It will be seen that the base of the lung has re-expanded very readily, but that the apex remains collapsed, probably because the diseased lung in this region has become converted into a mass of fibrous tissue. Plate XIV shows the condition four

weeks later, that is, three months after the last refill. The base of the lung has now almost completely re-expanded, and the patient's condition remained good. It should be noted what a large amount of useful lung there is even after over two years' treatment. Plate XV shows the condition of complete re-expansion three months later.

The X-ray readily shows small amounts of liquid in the pneumothorax cavity, but the patient should be examined in the upright position, so that the liquid may be seen above the diaphragm. Plate XVI shows the presence of liquid, and an adhesion above it to the axilla. It is in cases such as this that there is a great tendency for the fibrous tissue to contract and the pneumothorax cavity to be obliterated when the liquid is removed or absorbed. These cases, therefore, should repeatedly be examined with the X-ray, so that refills may be given and the intra-pleural pressure raised when necessary, or adhesions divided.

Plate XVII shows a localized pneumothorax cavity partially filled with liquid, but with an air-space above.

It is by means of the X-ray that the position of the mediastinum can be accurately determined. It is important to avoid much displacement of the mediastinum. Plates II and III, taken before and after removal of the liquid, show great displacement of the mediastinum, but Plate IV shows how the mediastinum can be brought back to its proper position by treatment. (See Chapter VIII.)

When there is a positive intra-pleural pressure the diaphragm of that side sometimes moves upwards with inspiration and downwards during expiration. This is known as Kienbock's phenomenon, and probably is due to the diaphragm being pushed upwards by the increased abdominal pressure during inspiration. Under the X-ray this gives the appearance of a see-saw movement to the diaphragm, one side moving in the opposite way to the other. I have found this phenomenon to be present in only a few of my cases. Generally both sides of the diaphragm move upwards or downwards at the same time, although the movement on the pneumothorax side is less than on the other.

Chapter XII.

Results of Pneumothorax Treatment.

Examination of the results of this treatment presents many difficulties. In the first place many patients with pulmonary tuberculosis are not advised to have artificial pneumothorax treatment until their condition is hopeless. To judge the value of the treatment from such cases would be like judging the value of appendicectomy if the surgeon were called in only when there was general peritonitis and the patient moribund.

Again, pulmonary tuberculosis is a disease of long duration and arrest without any treatment is not uncommon. To be certain that the apparent cure is because of, and not in spite of, any given

treatment one must divide the cases into types, and compare the results of each type with the various methods of treatment.

In 1913 Saugman gave the results of 100 sanatorium cases with less than half the better lung involved. Of these 64 had artificial pneumothorax. In the other 36 no effective pneumothorax could be made. Thus 64 had pneumothorax and sanatorium treatment; 36 had sanatorium treatment alone:

	Of the 64 cases.	Of the 36 cases.
Able to work	50 per cent.	22·2 per cent.
Unable to work	28·1 ,,	33·3 ,,
Dead from tuberculosis	18·7 ,,	38·8 ,.
Free from tubercle bacilli	50 ,,	8·6 ,,

In 1921 Saugman published further results. Of 257 cases of pulmonary tuberculosis in Group III of Turban's classification pneumothorax was induced in 172. In the other 85 cases the attempt to induce a pneumothorax failed. All these patients were discharged from the Veljlefjord Sanatorium between 1907 and 1916, and the following table shows their condition in 1919 :

	Of the 172 cases.	Of the 85 cases.
Able to work	32 per cent.	10·6 per cent.
Unable to work	2·9 ,,	3·5 ,,
Died from tuberculosis	63·4 ,,	83·5 ,,
Tubercle bacilli disappeared from the sputum	39 ,,	12 ,,

In comparing this with the previous table it must be remembered that these latter were Turban III stage cases. In both tables the pneumothorax cases are seen to have done better than the others.

Saxtorph (1921) has published an analysis of 200 cases treated at the Nakkebölle Fjord Sanatorium. Of these, the attempt to induce a pneumothorax failed in 58, succeeded in 108, and in the remaining 34 only a partial and inefficient pneumothorax could be induced :

Two years after discharge.	Of the 58 cases.	Of the 34 cases.	Of the 108 cases.
Able to work	5	2	{ 50
Unable to work	6	1	
Dead	47	27	58
Unknown	—	4	—

In addition to the 58 deaths of pneumothorax cases within two years of discharge, 13 died later, but of the total 108 cases 34 were alive from two to six years after discharge and most were at work.

I have divided my cases into the following groups for purposes of analysis :

Group A. Patients with little or no powers of resistance, and a rapidly spreading acute infection.

Group B. Patients with very good powers of resistance, and in the early stage of the disease. I have only two cases in this group and pneumothorax would not have been made but for repeated haemoptysis.

Group C. Patients with medium resistance who have failed to improve after other treatment. This group is subdivided into—1. The early stage where only one lung is involved.

2. The middle stage where there is disease in the better lung. 3. The advanced stage, where a third or more of the better lung is involved.

Group D. Non-tuberculous cases.

Tubercle bacilli were found in the sputum before treatment in every case except those in Group D.

The following tables show an analysis of my first 150 cases arranged according to the above groups. By arrested is meant disappearance of symptoms and of tubercle bacilli from the sputum for at least six months. It should be stated that some of these patients are still under treatment, and in some the treatment has only recently been stopped, so that the final result is unknown.

TABLE I.—*Cases in which an efficient pneumothorax was produced.*

	Group A.	B.	C 1.	C 2.	C 3.	D.	Total.
Arrested	—	2	27	4	—	7	40
Better	—	—	13	6	1	2	22
No change	—	—	1	6	2	3	12
Worse	—	—	—	7	6	—	13
Dead	3	—	2	3	9	3	20
Total	3	2	43	26	18	15	107

TABLE II.—*Cases in which only a partial and insufficient collapse was produced, and treatment was continued for less than two months.*

	Group A.	B.	C 1.	C 2.	C 3.	D.	Total.
Arrested	—	—	—	—	—	—	0
Better	—	—	2	1	—	—	3
No change	—	—	2	1	—	—	3
Worse	—	—	—	1	—	—	1
Dead	2	—	1	2	7	1	13
Total	2	0	5	5	7	1	20

TABLE III.—*Cases where pneumothorax could not be produced owing to adherent pleura.*

	Group A.	B.	C 1.	C 2.	C 3.	D.	Total.
Arrested	—	—	—	—	—	—	0
Better	—	—	2	—	—	—	2
No change	—	—	4	2	—	—	6
Worse	—	—	1	5	—	1	7
Dead	2	—	1	—	4	1	8
Total	2	0	8	7	4	2	23

It is in Groups C1 and C2 that the results are most striking. We know that a definite proportion of patients coming to an out-patient department with pulmonary tuberculosis eventually recover, and that this proportion is higher amongst those that are well-to-do. But the percentage of recoveries amongst those who still have active pulmonary tuberculosis after sanatorium treatment is very small.

Noel Bardswell (1919), in discussing the Midhurst cases with tubercle bacilli in the sputum, says that of those who left the

sanatorium with tubercle bacilli still present the ratio of actual deaths to expected deaths was 21·8 for males and 31·6 for females. That is to say, the mortality rates were 21·8 and 31·6 times greater than those of the general population of the same ages. In the cases of those who had lost the tubercle bacilli before discharge the ratios were 6·5 for males and 7·7 for females.

It should be clearly understood that the analysis of these 150 cases must by no means be taken as a form of statistics. As such the figures would be most misleading. The table does show, however, that a large proportion of the cases lose tubercle bacilli. Indeed this is one of the great benefits of pneumothorax treatment. Tubercle bacilli disappear from the sputum of many patients treated by pneumothorax, even though the disease is not arrested. It will also be noted that acute cases do badly.

Dr. Vere Pearson (1919) gives the results of cases treated between August 1910 and December 1916. In 13 cases he was unable to induce an efficient pneumothorax ; of these 12 were dead and 1 a chronic invalid in 1919. The average length of life in the 12 cases was under 2 years. Of 21 cases in which an efficient pneumothorax was induced 11 were alive and 10 dead in 1919. Of the 11 the average time since the treatment started was $4\frac{3}{4}$ years, the longest $7\frac{3}{4}$, and the shortest $2\frac{1}{2}$ years. Of the 10 who died in spite of treatment the average length of life was $2\frac{3}{4}$ years, although included amongst these 10 cases are 3 who lived only $1\frac{1}{2}$, $4\frac{1}{2}$, and $6\frac{1}{2}$ months respectively.

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PART II.

REPORTS ON PERSONAL EXPERIENCE IN THE TREATMENT OF PULMONARY DISEASE BY ARTIFICIAL PNEUMOTHORAX.

CONTENTS OF PART II.

I. Introductory Note.

The induction of an artificial pneumothorax is being increasingly adopted in the treatment of pulmonary disease, and especially in the treatment of chronic pulmonary tuberculosis in this country. The bibliography of the subject is already extensive, and much has been added to our knowledge since Forlanini began his early experiments, which mark the beginnings of modern research into the efficacy of the method.

Hitherto, it must be admitted that this measure of tuberculosis therapy has been in the experimental stage, the inevitable probationary period that each advance in knowledge must pass through before it can receive general adoption. At the outset of this investigation we were already aware that in the hands of those who had specially studied artificial pneumothorax the results had been encouraging; it is scarcely necessary to refer to the illuminating works of Riviere, Saugman, and others on this point; but we required to know if these favourable results had been equally experienced by other workers, and whether a consensus of opinion could be elicited not only as to the value of the treatment but also as to its indications and contra-indications in cases of pulmonary disease.

At the same time we could not be unmindful, if reliable evidence were forthcoming as to the efficacy and limitations of artificial pneumothorax, and further, if such conclusions were expressed by those best qualified to speak on the subject, that by collating such evidence the treatment might well emerge from the sphere of experiment into the practice of Medicine. We hoped, therefore, that such a marshalling of expert opinion would serve not only as a work of reference to past essays in the treatment but might aid those who desired to be well assured of the feasibility, indications, and value of the method before employing or recommending it in their own practice.

This plan of investigation has been carried out through the kind co-operation of those physicians who have specially devoted their attention to artificial pneumothorax in this country, and who readily consented to give the Medical Research Council the results of their experience in a reply to a *questionnaire* which was sent to them. Certain of these physicians have been also so good as to make special observations on the value of the treatment in more detail or have referred us to their published papers and articles upon the subject.

In drawing up the *questionnaire* we had mainly in view an estimation of the value of artificial pneumothorax treatment, but inquiry was also made as to the number of cases treated by each worker. It was also important to discover what type of case was considered suitable, for a physician who had confined his attention mainly to the treatment of very advanced cases of chronic pulmonary tuberculosis might well hold a different view as to the

value of the treatment from one treating more early and favourable cases of the disease.

Furthermore, we deemed it necessary to inquire into certain matters of technique in order to discover whether the opinion as to the value of the treatment varied with any special point in operative procedure. We are and always have been of opinion that close attention to details, and the treatment of each patient as an individual, make all the difference as to results.

Lastly, in order to weigh the advantages with the disadvantages of this method of treatment information was sought as to the accidents and complications encountered.

L. S. T. B.

A. S. M.

II. COPY OF LETTER SENT BY THE SECRETARY OF THE TUBERCULOSIS COMMITTEE TO THE PHYSICIANS REPORTING ON THE VALUE OF TREATMENT OF PULMONARY DISEASE BY ARTIFICIAL PNEUMOTHORAX.

Dear Sir,

MEDICAL RESEARCH COUNCIL.

Tuberculosis Committee.

This Committee are undertaking an investigation into the treatment of pulmonary tuberculosis by artificial pneumothorax.

The Committee would greatly value your aid in this investigation, and I should be grateful if you would reply to the enclosed *questionnaire* and return it to me with your answers.

Any further remarks or observations which you may care to make upon this form of treatment I shall have pleasure in submitting to the Committee.

Yours faithfully,

(Sgd.) A. SALUSBURY MACNALTY.
Secretary to the Tuberculosis Committee.

III. COPY OF QUESTIONNAIRE.

MEDICAL RESEARCH COUNCIL.

TUBERCULOSIS COMMITTEE.

Treatment of Pulmonary Tuberculosis by Artificial Pneumothorax.

1. State the number of cases you have treated by artificial pneumothorax.
2. What are (*a*) the indications for the operation, (*b*) the contra-indications?
3. What effect do you consider a pneumothorax has upon the other lung?
4. Have you performed a pneumothorax on both sides in the same patient at different times? If so, in how many cases?
5. What accidents or complications have you experienced in the treatment, and what steps do you take to prevent them?
6. Have you obtained good results in cases with adhesions?
7. Have you any observations to make upon the technique or the apparatus employed? Do you employ a local anaesthetic?
8. In what percentage of cases have you failed to produce a pneumothorax?
9. Do you consider the choice of gas important?

10. Do you advocate a small or large initial quantity of gas? Have you observed any bad effects after a large quantity of gas has been given?

11. What pressure do you obtain (a) after the initial operation, (b) when the lung has been well collapsed?

12. What is your opinion as to the value of the treatment?

IV. Reports on Personal Experience in the Treatment of Pulmonary Disease by Artificial Pneumothorax.

1. Report by H. O. Blanford, M.B., B.S., *Medical Superintendent, King Edward VII Sanatorium, Midhurst.*

Reply to Questionnaire.

1. Eighteen cases.
2. (a) Failure of ordinary sanatorium régime in reducing temperature and improving symptoms; (b) bilateral activity. Pleural adhesions.
3. Insufficient experience to form an opinion.
4. No.
5. None.
6. One case; incomplete collapse, but marked improvement.
7. The simpler the better; too fine a needle, easily blocked. Yes, always. Endrenine.
8. Twenty-one per cent.
9. I always use air.
10. Small; frequent refills; dyspnoea and general discomfort.
11. (a) About zero. (b) About +20.
12. In my opinion the treatment is of value in those cases in which the disease as shown by physical signs and X-rays is chiefly or entirely unilateral, and in which ordinary sanatorium methods of absolute rest, fresh air, &c., have failed to effect an improvement. Its practical value is likely to be more marked in the well-to-do class which can afford a prolonged period of leisure and the expenses of journey and accommodation inseparable from the process of refills.

2. Report by Esther Carling, M.D., Brux., *Chief Medical Officer, Berks and Bucks Joint Sanatorium.*

Reply to Questionnaire.

1. Sixty-seven cases.
2. (a) One-sided progressive disease with bad prognosis.
   (b) (1) Demonstrable disease in better lung; (2) Sometimes hypersensitive nervous condition; (3) Circumstances which make prolonged treatment impossible.
3. In case 5 of my series. Better lung 'lit up'. Rapid downhill progress.
   In case 58. Better lung began to show signs of involvement clinically and by X-ray. Compression stopped, patient improved, now doing well (six months later).
   In case 61. Signs developed in the better lung. Compression stopped, patient improved.
   In case 63. Natural pneumothorax developed in better lung after violent coughing. Questionable as to whether this was in any way a result of compression of other lung, but result was fatal within a week.
   These four are the only cases in which a definitely bad effect on the other lung has been noted.
4. No.
5. *Accidents.* No serious accident has occurred.
   Three cases of *pleural shock* have been noted. In each there was a condition of momentary rigidity with livid colour and quickened pulse, described

by a nurse as 'a fit' and not unlike that. In one case strychnine was injected; in the others the patient had 'come round' before treatment could be given. No after-effect.

Natural Pneumothorax occurring after artificial compression.

(1) See case 63 noted above.

(2) Case 39. This man had resumed full work as a chauffeur. While winding up a heavy car felt sudden pain and sense of 'something giving way'. Became acutely ill, hydro-pneumothorax developed, died eventually.

Complications. A very frequent complication is pleural effusion.

In 17 cases the occurrence of fluid has stopped further treatment. I have not found it satisfactory to remove fluid and inject gas simultaneously. It seems better to let the fluid keep up the compression.

In case 12 fluid developed after two years' treatment, the chest wall fell in, and compression has been maintained without further injections for over three years. Patient is well and at work.

In cases 52 and 67 fluid developed within two or three weeks of beginning treatment; case 52 went slowly downhill; case 67 has improved steadily.

I imagine that fluid occurs in so many cases as a result of irritation, and have found no way of preventing it. As a rule it is a fairly late complication, but may occur at any time.

6. (I. e. partially established cases.) They are nearly always unsatisfactory.

7. *Technique.* Iodine before and after punctures; needle and stylet kept in absolute alcohol and carefully dried in flame before use. Position of patient carefully adjusted with a view to (1) comfort during operation; (2) space between ribs.

A quick thrust through stretched skin produced least pain. A skilled nurse watches pulse all through operation, and has an eye on patient for some quarter of an hour after. (Shock once occurred 10 minutes after an easy injection.)

Apparatus. Lillingston's, modified by glass tap to turn gas on and off. Saugman's short needles used.

Local anaesthetic employed on the first two occasions only.

8. 19.4 per cent. (13 out of 67).

9. No. I use oxygen for the first operation; afterwards nitrogen or filtered air.

10. I attempt 300 c.cm. for the first one or two inflations; afterwards only such amounts as produce a small + pressure. I never give more than 1,000 or 1,100 c.cm.

'Bad effects' are more a result of pressure attained than actual amount of gas given.

11. (*a*) I aim at slightly reducing the negative pressure found before gas is inserted. Thus if pressure originally found is, say. 12–18, I should consider a pressure of 10–14 after 300 c.cm. of gas very satisfactory.

(*b*) A pressure of 0 and + 6 at the end of refills maintains a satisfactory result. or even less.

I am afraid of high pressures.

12. See following report.

REPORT ON THE VALUE OF ARTIFICIAL PNEUMOTHORAX. IMPRESSIONS AFTER EIGHT YEARS AND FIFTY-FOUR CASES.

(Extract from an article published in *Tubercle*, 1920, **1**, 411.

This treatment has only been attempted in cases that were doing badly on ordinary lines and in whom therefore the prognosis was unfavourable; all have been either in the advanced or acute stage, and all presented more or less unilateral disease. In 12 of the 54 cases it was not possible to establish the treatment (in 10 cases because free pleural space could not be found, and in two because of the nervous apprehension of the patients). In 42 cases a pneumothorax was more or less completely established and the treatment was continued. At the end of eight years, reviewing all the cases, it is

found: of the 42 in whom the treatment was established 21 are dead; 22 showed marked improvement after treatment, of these eight are dead, 13 have returned to their old occupations or to a moderately active and useful life, one is going downhill.

The 22 cases represent the best results of a treatment undertaken when all else seemed hopeless, and in the eight cases which eventually died certain of them became temporarily not merely better but practically well. Of the remaining 20 cases, 12 are still undergoing treatment or have finished it too recently to classify (i. e. less than one year); eight were unaffected, i. e. the disease went on without apparent check. In two of these cases it is possible that the inevitable end was hastened rather than hindered by the compression treatment. In one the 'good lung' gave way and an acute process set in which quickly ended a patient worn with many years of chronic disease. In this case the treatment was deliberately chosen, though the risk to the more sound of the two lungs had been pointed out.

The other case was unpromising but of fairly recent origin. Three months after starting the compression the patient for domestic reasons left the Sanatorium. A week after returning home she became acutely ill. Her doctor asked me to see her and I found signs of an effusion in the pleural cavity in addition to acute abdominal symptoms. Death followed quickly.

Before beginning the treatment it is desirable fully to advise patients and their friends that it may not be possible to get the compression established in order that the choice on their parts may be a deliberate one. Sometimes this means a refusal to undergo treatment, but that is a lesser evil than recrimination. The first three cases of this series were started at St. Mary's Hospital by Dr. Leonard Colebrook, who kindly allows me to include them, as their subsequent treatment was continued at the Berks and Bucks Sanatorium. Most of the rest were undertaken in co-operation with Dr. Claude Lillingston, who introduced the treatment to this country.

The treatment seems to have its best chance in a Sanatorium where it can be kept going and where encouraging object lessons are always at hand. No other procedure offers as good a hope of improving the dreary lot of an advanced case of phthisis as does the successful induction of an artificial pneumothorax.

Further Note on Additional Cases treated in the years 1920, 1921, and 1922.

Artificial pneumothorax attempted 25
,, ,, established 22
,, ,, not established 3

Of the 22 established cases,

Three have returned to work,
Three are living at home improved in health.
Seven are dead.
Nine are still under definite treatment.

Marked initial improvement occurred in 10 of the 23 established cases. No definite change occurred in 10 (owing to early development of pleural effusion, presence of adhesions, too early giving-up of treatment, &c.) Three are too recent to report upon.

3. Report by **H. Morriston Davies, M.A., M.D., M.Ch., F.R.C.S.,** *Vale of Clwyd Sanatorium, Ruthin, North Wales.*

REPLY TO QUESTIONNAIRE AND OBSERVATIONS.

1. About 90 cases.

I have full details only of the cases done in the last $2\frac{1}{2}$ years. They number 50, and it is on them only the following figures are given:

A. Treatment being continued with, 24 (48 per cent.).
No case has completed treatment.
B. Failed to produce a pneumothorax, 6 (12 per cent.).
C. Pneumothorax obtained but abandoned after periods varying from one to five months owing to difficulties from adhesions and inadequacy of collapse, 7 (14 per cent.).

D. Abandoned because disease progressed despite treatment, 7 (14 per cent.).

In all these cases except one the treatment was done as a 'last resort' measure, and there was some disease in the opposite lung. In one only was anything like a complete collapse obtained.

In the exception case the patient did extremely well, but after being back at work over six months, the opposite lung began to show signs of infection. This progressed and the suggestion to allow the collapsed lung to re-expand and to produce collapse of the other lung was not agreed to.

E. Abandoned for other reasons, 6 (12 per cent.).

2. (a) *Indications for the operation.*

In my opinion, no case is too 'early' for this method of treatment. An 'early' case does not mean that the patient has got a good resistance and will therefore respond and obtain permanent or even temporary benefit by the ordinary hygienic methods of treatment. 'Early' and 'good powers of resistance' are not synonymous terms, though they are often used as such.

It may be said therefore that every case in which there is no definite contra-indication is a suitable one for artificial pneumothorax treatment.

Special indications are :—Haemorrhage. Cavities. Pneumonic Tubercle. Tuberculosis of the lung and larynx. Pulmonary tuberculosis in young adults. Pulmonary tuberculosis in those who have to return to an unsuitable environment. Pulmonary tuberculosis in those who have to mix with fellow workers indoors. Pulmonary tuberculosis in those whose work is connected with foods. Pulmonary tuberculosis in mothers with young children. When other means have been tried and have not proved successful, or when the disease recurs after arrest.

(b) The *contra-indications* are :—Extensive disease in the opposite lung. At least two-thirds of the opposite lung should be healthy. (See also reply to Question 3.) Tuberculous enteritis. Tuberculous gland sor extensive disease elsewhere (except in the larynx). Renal or cardiac inadequacy or disease. Elderly people who show a reasonable power of resistance. Generalized bronchitis, asthma, bilateral secondary infection. People highly strung or of an extremely nervous disposition.

3. A. When the other lung is healthy. I have no evidence indicating that emphysematous or any other changes occur in the 'other lung'.

B. When the 'other lung' is diseased. I divide the disease into two types :

1. Secondary. When it is a definite localized peribronchial lesion. In such cases, collapse of the 'one lung' has almost always a beneficial effect on the 'other lung'.

2. Primary. When the distribution of the disease in the 'other lung' is such that the indications suggesting that the disease is merely a spread from the 'one lung' are absent, improvement in the 'other lung' may or may not take place. It depends then on the general resistance of the patient and on whether the control of the disease in the 'one lung' will allow of a sufficient increase in the 'health resistance' to enable the patient himself to deal with the disease in the 'other lung'.

4. Yes, in three cases. (Two only out of the 50.)

5. *Complications and accidents.*

A. *Reactions.* 1. Pure tubercular reaction. 2. Coli or streptococcal toxaemia reactions. 3. Mixed reaction.

The last two are far and away the most serious and are due to a toxaemia from the intestinal tract as the result of intestinal stasis. The organism is generally the *Bacillus coli*, and in these cases sulpho-ethers will be found in the urine in large quantities and, almost invariably when nausea is a symptom, acetone as well. Less commonly, the secondary infection is due to the streptococcus, and the temperature chart is almost diagnostic, whilst traces only of sulpho-ethers, if any, are found in the urine. The reactions in these cases are of a much more serious nature,

and may be so prolonged that the artificial pneumothorax has to be abandoned (i. e. in those cases in which the cause is not recognized and treated). In this Sanatorium, the urine is constantly tested for sulpho-ethers. When a patient is found to be suffering from chronic intestinal stasis and to be liable to exacerbations of intestinal toxaemia, calomel or castor oil is always given as a preliminary to an injection of gas. The effect of this is to reduce and frequently to abolish all reaction.

Streptococcal cases are treated by vaccines.

The pure tubercular reactions are controlled by the amount of gas introduced.

B. *Pleural effusions.* There are six causes of fluid: 1. Systemic infections. *B. coli* is the commonest organism. Less usually it is pneumococcus and streptococcus, or it is a complication of influenza. 2. The irritation due to adhesions. 3. Direct infection at the operation. 4. Indirect infection or direct infection from an infected sinus in the chest wall. 5. Infection as a result of spontaneous pneumothorax. 6. Tubercular infection. (One case only in this series: no case under groups 3, 4, and 5.)

The liquid may be sterile or apparently sterile; it may be infected, i. e. containing demonstrable organisms. The liquid should always be removed because of (1) its effect on the patient, producing a very decided feeling of malaise and possibly chronic fever. (2) The tendency of adhesions to form or the lung to become incapable of re-expansion owing to the thickening of the visceral pleura. (3) The risk of secondary infection. Unless the liquid subsides rapidly and shows no tendency to recur, it should be removed and the liquid and part of the gas in the pleural cavity replaced by oxygen, and when the liquid has ceased to recur, the pneumothorax maintained by nitrogen.

C. *Infection of the track of the needle.* I have frequently seen infection of the track of the needle. As yet it has never occurred in any of my patients under treatment for simple artificial pneumothorax, and should not occur if the proper aseptic precautions are taken.

D. *Spontaneous pneumothorax.* On two occasions, a comparatively slight spontaneous pneumothorax has occurred within two days of a refill on the same side as the artificial pneumothorax. In both cases the lung was in part adherent, but no bands of adhesions could be seen by the X-rays, and a small positive pressure only had been left. The increase in pressure in neither case was sufficient to necessitate active steps being taken. In one case the pneumothorax had been maintained for about nine months, and in the other for about two years previously.

E. *Displacement of the mediastinum.* This should never occur to an extent to cause serious complication, if the treatment is properly controlled by the X-rays. One patient, however, was sent to me with the mediastinum extensively displaced. He had been having refills every month (though his pneumothorax had been maintained over three years); after each of the last few refills he had suffered from what was obviously acute kinking of the bronchus to the sound lung. I allowed him to go four months without a refill and there has been no return of these symptoms.

F. *Bulging of the right vertebro-mediastinal pleural sinus to the opposite side.* I have seen this in two cases. In one, after the development of a spontaneous pneumothorax. In the other, it was noticed after a refill in which the intra-pleural pressure had been raised to $+7$ mm. of mercury (the same as on previous occasions), but at which I was surprised to find that he required 200 c.cm. more gas than previously without there being any reason to account for it. This patient had been 'X-rayed' after each refill and there had been no previous indication of this state of affairs. The only symptom was a slight increase in shortness of breath.

G. *and* H. *Pleural reflex and gas embolism.* The non-occurrence of these complications in my cases, I attribute partly to the fact that I always take precautions against them. Against the former by anaesthetizing the track of the needle, and against the latter by using oxygen instead of nitrogen if I am doubtful whether I am in the pleural cavity.

(Total punctures in the 50 cases about 750.)

6. Yes. Provided that a collapse equal to half the lung can be obtained. When the adhesions are such as to allow of it, I stretch them by maintaining a fairly constant pressure on the lung. When this is dangerous owing to the condition of the lung at the point of attachment of the adhesion, or stretching is impossible, I divide the adhesion, if division is practicable. Lungs which are adherent over the posterior surface show a peculiar tendency to creep out between the refills, gaining fresh points of attachment, and after six to 12 months reduce the pneumothorax space beyond the limit to which it is of any value.

7. The essential points about *the apparatus* are :—A. That it should be capable of manipulation by the operator with one hand, leaving the other free to hold the needle. B. That it should be capable of delivering the gas at any speed required, the importance being slowness at the onset. C. That the manometer should be a water one, easily visible. D. That the apparatus should be capable of delivering either oxygen or nitrogen. E. That the filter and the parts between it and the needle should be easily sterilized. F. Portability.

   I have never given an injection without giving two per cent. novocain.

8. 12 per cent.

9. Yes. I always use nitrogen, because oxygen is so rapidly absorbed. If air is used, the oxygen out of it will be absorbed much more rapidly than the other gases. Roughly speaking, 500 c.cm. of air are equivalent to 420 c.cm. of nitrogen (allowing for the replacement by intra-pleural interchange of gases of the 100 c.cm. of oxygen in the air by 20 c.cm. of nitrogen and CO_2), whilst the reaction produced is equal to $\frac{500}{420}$.

10. I rarely use more than 200 c.cm. as the initial quantity of gas. I have seen very severe reactions occurring with larger doses.

11. It is impossible to answer this question, for in my experience no two patients who can be meted out the same consecutive measures of gas will show the same pressures or give the same reactions.

    (a) If the pleural cavity is free of all adhesions, the pressure obtained at the end of the initial operation will certainly be negative, but the inspiratory pressure may vary from one equal to -9 mm. of mercury, whilst the expiratory may vary from -6 mm. of mercury to -2. When adhesions are present, the pressure at the end of the initial operation may be negative or positive. When there is an exudate of lymph between the two surfaces, the expiratory pressure will be positive, but the inspiratory pressure will be either negative or positive. At subsequent injections both may become negative.

    (b) When the lung is completely collapsed in the absence of adhesions, the inspiratory pressure is usually in the neighbourhood of zero, whilst the expiratory will vary from about $+4$ mm. of mercury to about $+8$ mm. of mercury. The highest pressure which I have left when adhesions have been present was one equal to 33 mm. of mercury.

12. My opinion is that this method of treatment is by far the most valuable one we possess for arresting the progress of pulmonary tuberculosis.

    I have never as yet regretted doing an artificial pneumothorax, but I frequently have had occasion to regret that I did not more strongly urge this line of treatment to some patients, or that, because I found the patient progressing so well under the ordinary régime of sanatorium treatment, I was myself dissuaded by this fact from recommending artificial pneumothorax.

    I have treated about 18 per cent. of the patients I have had since I have been here by artificial pneumothorax. Of the 82 per cent. not so treated, the bulk have been too advanced (by this I mean that both lungs have been too extensively involved for this treatment). In a few there have been other contra-indications. 0·32 per cent. of patients have refused treatment.

    If only this disease were recognized earlier, and if only this line of treatment were more universally (and efficiently) carried out, I believe that the additional number of lives that could be saved, and the number of people that could be returned fit for their employment, would be enormous.

    The importance of constant control of the collapse by X-rays cannot be over-emphasized. It is essential to guard against injurious displacement of the

mediastinum, or bulging of the pleura to the opposite side; to recognize the variety and character of the adhesions and whether attempts at stretching may be tried with safety; to recognize the presence of small quantities of fluid; to note the degree of re-expansion of the lung before a refill, and whether a collapse is as complete as it should be after a refill.

No artificial pneumothorax should be started unless the condition of the 'other lung' has been checked by X-ray observation, unless such is impossible (and it should be possible in all institutions).

4. Report by the late **H. G. Felkin, M.D.,** *Linford, Ringwood, Hants.*

REPLY TO QUESTIONNAIRE.

1. We have attempted to produce a pneumothorax in 24 cases, succeeded in 19 and failed in five. Of the successful cases eleven were on right and eight on left side.
2. As regards this we agree entirely with the indications set forth in Dr. Clive Riviere's book.
3. Generally beneficial: in a few desperate cases, done as a last resort, with probably activity in the better lung, the activity in the other lung was increased.
4. No, never.
5. None at primary puncture, except unimportant subcutaneous emphysema. Five of the 19 cases developed clear serous effusions and two further ones purulent effusions.
6. Certainly in a considerable number of cases.
7. We use what is generally known as Lillingston and Pearson's apparatus with a water manometer and either Clive Riviere's needle for primary puncture or a Saugman's needle with external opening as near point as possible and not too sharp.
8. In 20·8 per cent. of cases; see above, No. 1.
9. No, we use nitrogen. Probably if sterile air is used the pressures fall sooner as the oxygen is quickly absorbed.
10. We generally give initially 400-600 c.cm. of nitrogen, mostly not over 500 c.cm. We have seen no ill effects and have never exceeded 600 c.cm. N_2 at first puncture.
11. (a) This varies greatly with the extent of pleural adhesions. With high original negative, say -18 to -12, we should leave off at -14 to -8 probably: with low original negative we might leave off with expiratory reading at zero.
    (b) This also varies greatly. We have with benefit maintained pressures of $+45$ to $+50$ for some time. The average would be $+6$ to $+12$.
12. For *carefully selected cases* the value of the treatment is very great and will give results obtainable in no other way. It can restore apparently hopeless cases to almost perfect health and usefulness. In other cases it will much prolong life and give some months or years of fairly happy life and comparative health.
    Note. We did one case by Brauer's method of open incision under local anaesthetic down to the pleura, but we see no advantage in this over the puncture method.
    Note to Question No. 7. We now always use a local anaesthetic for initial punctures and generally for early refills.

5. Report by **Z. P. Fernandez, B.A., M.D.,** *Honorary Assistant Physician, Armley Sanatorium, Leeds.*

REPLY TO QUESTIONNAIRE WITH OBSERVATIONS.

1. *Number of cases treated.* First series of 50 cases analysed in *Practitioner*, June 1920, being cases from 1917. Conditions of cases as stated then with 29 deaths. Second series of 56. Of these 21 died, one being by street accident. Third series of 28 cases with four deaths. Conditions satisfactory

in the surviving cases with few exceptions. Total 134 cases, with 54 deaths, excluding cases mainly under Dr. Woodcock, for whom I have done refills occasionally.[1]

N.B.—Cases of 1 or 2 or 3 inductions not included.

2. *(a) Indications.*

1. *Severe and continued haemoptysis.* If bilateral disease and site of lesion are not evident, the side with more moist signs is tried with a small amount of gas, and if condition persists success may follow treatment of the other side. As a rule the patient will give you the indication; he generally lies on the non-bleeding side ; systolic and pulse pressure taken with Tycos's sphygmomanometer I have found greater on the bleeding side during haemoptysis and lowered after pneumothorax treatment. Blood-pressure lowered in ordinary induction cases soon after operation generally improves when condition gets better.

2. *Continued pyrexia over* 100° F. *a.* Unilateral disease with severe or moderate systemic disturbance and fair resistance. *b.* Bilateral disease with more extensive disease on one side, systemic disturbance, and fair resistance.

3. *Apyrexial cases. a.* Unilateral cases with extensive disintegrative signs and systemic disturbance. *b.* Bilateral cases with sufficient healthy lung on either side with moderate systemic disturbance and good resistance. Bilateral induction with small amount of gas in experienced hands may be beneficial ; if pyrexia is present it improves.

4. *Abscess or gangrene of lung.*

5. *Bronchiectasis* in adults or children with haemoptysis. A girl of school age improved remarkably in 1918.

6. *Certain types of primary pleural effusion and tuberculous empyema.* By aspiration and oxygen induction I have now treated 6 cases.

7. *Post-operative continued discharging sinus of tubercular empyema.* Three cases treated. One arrested ; one died. The other treated by pneumothorax since November 1920. She was operated upon ten months previously ; profuse discharge ever since, bedridden all the time. I have given her so far 12 inductions in her own home as a domiciliary case in co-operation with her medical attendant. She has so much improved that she has been enabled to visit her home in Belgium for a holiday. There was then a little occasional thin discharge which later subsided. A culture made from the pus grew the tubercle bacillus. With my old apparatus there was difficulty in induction ; not so with our newer apparatus. Partial immobilization with later re-expansion of lung is an advantage when induction is possible as compared with thoracoplasty.

8. *Case of recent onset with progressive activity not reacting to sanatorium treatment.*

2. *(b) Contra-indications.*

1. Extensive bilateral disease with severe systemic disturbance and poor resistance in which a hopeless prognosis is evident.

2. Marked fibrosis with chronic bronchitis and emphysema.

3. Pulmonary tuberculosis associated with—*a.* Intestinal complication and diarrhoea, &c. *b.* Advanced laryngeal ulceration. Slight or moderate disease may be benefited. *c.* Multiple cold abscess. I have known cases treated with large dosage formerly develop multiple abscesses, for which the patients blamed pneumothorax treatment. During the last three years I have not come across such cases. *d.* Cardiac valvular or myocardial degenerative or cardio-vascular disease. Early tuberculous tachycardia or toxic dyspnoea not a contra-indication and often benefited. *e.* Other severe illness or malignant disease. *f.* Chronic nephritis.

4. Cases of neurotic tendency or mental stigma.

5. Asthmatics.

6. Generalized or acute miliary tuberculosis.

[1] See also ‘ 16. Report by Dr. H. de Carle Woodcock ’, p. 86.

7. Cases with initial negative pressure of less than one cm. water with little respiratory oscillation, which repeated show no satisfactory alteration. I have, however, known cases with little negative pressure with induction improve and give satisfactory oscillation and an increased negative pressure.

3. *Effect on other lung.* As a rule, if induction of 300 to 500 c.cm. of gas is only given at regulated intervals, and the intrapleural pressure thereby altered only two or three cm. of water and kept within negative limit, no harm is done to the other lung. In my first inductions of large dosage I considered that one or two unilateral cases developed bilateral disease. In two cases of severe haemoptysis after the condition subsided, haemoptysis occurred with acute disease of the other lung as revealed by the necropsy; in one case after the patient had considerably improved for a long time. Probably a bilateral small induction might have been beneficial.

4. *Bilateral pneumothorax* in the same patient. Six cases as published in *Practitioner*, June 1920. Three still alive. In my latest series six cases. Of these four are doing well, and two in whom pyrexia was controlled died recently. Bilateral induction needs careful selection and should be attempted only by an experienced worker. No doubt in some cases it has its value. Dosage also should be small.

5. *Accidents or complication.* No accident in my first 50 series. Only in one of these cases pleural effusion developed, which was successfully treated by aspiration and oxygen replacement. This was one of my large dose cases. He died later from influenza during the epidemic in 1918. Occasionally I noticed in the days of large dosage more pain than now met with and a little dyspnoea on the night of induction. A case of severe haemoptysis who refused treatment for a long time in spite of recurrence died the day after he had a small induction from sudden haemoptysis. The impression of the case at necropsy was that earlier induction and repeated dosage might have prevented the fatal termination. In my second series, on 10th February 1920, at the fifth induction a patient, soon after the novocain and adrenalin was put in, complained of dizziness, haziness, and lost the use of the right arm for three minutes. The pupils were slightly dilated and a squint was observed. His heart was massaged, strychnine injected, hot bottle put on, and brandy given. He soon came round, though no gas was given. He was treated on the left side. He gave a history of fainting on three occasions after a knock. Subsequently he had six inductions, and his pulmonary disease was so quiescent as to permit of his working as a porter at the sanatorium for some time. Later he caught a 'cold', developed typical signs of tuberculous meningitis about the middle of October, and died 13th November 1920. Lumbar puncture was done three times, and the cerebrospinal fluid gave a good positive culture on gentian violet egg-broth medium of the tubercle bacillus.

A case of pleural reflex occurred under other hands about the same time, and we had reason to fear the novocain solution used then was not satisfactory. Recently a second pleural effusion has occurred. After aspiration once with oxygen replacement he showed no evidence of fluid by X-ray, and pyrexia subsided. He is now doing well and has refills. He told me afterwards that before he came for the induction he ran for a car and came in sweating; later he developed a pleural effusion. I have seen surgical emphysema caused in other hands by want of patience, and by injecting gas when the respiratory fluctuation was not evident. I have heard of painful induration produced by quinine urea; I never use this form of local anaesthesia.

Precautions. Do not attempt more than three punctures on the same day.

See the water used is tepid and not too cold.

Always use a local anaesthetic as given below.

Never force gas in single manometer without sufficient respiratory fluctuation.

I do not give massive doses. I have seen cardiac mediastinal displacement and extreme dyspnoea after large doses of 1,500 c.cm. and more.

To carry out the treatment satisfactorily one must have plenty of patience ; one should not be in a hurry, and must gain the confidence of the patient.

Never use a high positive pressure in injecting gas.

6. *Good result in cases of adhesions.* In my first series in about 18 per cent., mostly bilateral disease, I could not continue the treatment and considered them as cases of adhesions, who eventually died. However, I have on later occasions succeeded with such cases. I am of opinion the instrument is at fault occasionally. For the last seven or eight months I have only used the modified apparatus with double manometer and differential pressure regulator in the form of a screw shunt, in devising which I have been associated with Dr. Woodcock, bringing to his notice Dr. Parry Morgan's throttle and his suggestions. I cannot, however, endorse all Dr. Parry Morgan's findings. Our apparatus needs no calculations. Suffice it to say that in cases in which previously I could not give gas for want of respiratory fluctuation I have always succeeded with the newer pattern. In empyema cases I should always prefer the modified apparatus. Thus good results have been obtained in cases one would otherwise consider as cases of inoperable adhesions.

If during induction a negative pressure becomes still more negative after gas-flow, it is an indication that the adhesion has been separated. This has often been noticed in the use of our newer apparatus.

7. *Technique, &c.* The single-needle method Dr. Woodcock used two years ago, and which I have adopted ever since, with practice is the best. It not only saves two pricks, but lessens the traumatic effect of the stouter needles we used before. I use a Record syringe needle for injecting one c.cm. of warmed novocain 2 per cent. with adrenalin in 1 in 10,000 after freezing with ethyl chloride spray. The needle is not then removed and chest tube connected.

Fuller particulars of our newer apparatus Dr. Woodcock and myself hope to publish shortly.

Local anaesthetic always used.

8. About 18 per cent. in my first series. With newer apparatus I have never failed so far. even with old cases in which I failed to succeed formerly.

9. *Choice of gas.* In my thesis and at the Leeds Congress, I have emphasized the value of oxygen. Dr. Benjamin Moore's view, quoted in my thesis, was from a personal communication. He considered oxygen has an inhibitory action on the tubercle bacillus. The supposed lessened absorption of nitrogen is, even if true, not an advantage so long as total collapse is not aimed at. The therapeutic value of oxygen has been well established. Nitrogen users, I have reason to believe, have had more cases of effusion than we have in Leeds. Purified air is equally good.

10. *Initial quantity of gas.* When the case is a suitable case, I always dispense with what Dr. Woodcock calls a preliminary manœuvre. So at first I give a dose of about 200 to 250 c.cm. gas. and avoid an unnecessary puncture. In a bad haemoptysis case, when the side is evident, I have given 500 c.cm. or more for the first induction.

11. The pressure after the initial operation will depend on the type of case. With a dosage of 200 c.cm. there will be an alteration of about only one or two c.cm. of water. I never aim at causing a positive pressure. In cases that have done well after two or three years one gets a good negative pressure. In others I have noticed pressure still negative, but slight. To give an instance, we radiographed a case after 12 inductions and found the lung collapsed to the border of the heart ; the patient gave a negative inspiratory rise of 10 c.cm. pressure. Manometric pressure observation is essential, but may vary with bore of the needle, bore of manometric tubing, site of puncture. type of breathing, and position of patient.

N.B. Higher positive pressures recorded by observers after a refill of 300 to 500 c.cm. of gas, in my opinion, are due in many cases to readings taken too soon after the gas-flow has been cut off. In these cases generally

a larger pressure is used for flow of gas towards the chest, which sets up momentum in manometer column showing an inertia of movement in the positive direction for a time, even when the original driving pressure has ceased to act.

12. Pneumothorax treatment is the only real advancement in phthisis therapy for the last 10 years. Those who have employed the method in well-selected cases have been so satisfied with the results as not to relinquish it. Again, statistics so far published in England and abroad, granting inaccuracy, all record beneficial results in 40 to 50 per cent. cases, after a reasonable interval, which otherwise would not have lived so long. In severe haemoptysis, which is a fatal but avoidable complication, the treatment can be relied on as for an operation for an abdominal emergency. Again, by lessening expectoration infection is prevented. It is an operation only to be undertaken by experts and not by novices. A bad operator may set the clock back for months; in a sanatorium, if a case went wrong, I for my part would blame the operator rather than the operation of pneumothorax.

The percentage of cases suitable is much higher than so far attempted in this country; though the treatment to have good results requires careful selection.

References to published papers by Dr. Fernandez on the subject.

(1) ' A Recent Analysis of Consecutive Induction of Artificial Pneumothorax in Fifty Cases of Pulmonary Tuberculosis.' *Practitioner*, 1920, **104**, 443.

(2) 'The Value of Artificial Pneumothorax in the Arrest and Prevention of Haemoptysis in Pulmonary Tuberculosis.' *Brit. M. J.*, 1918, ii, 55.

(3) 'Observations on Pneumothorax Therapy.' *British Journal of Tuberculosis*, Oct. 1921.

6. Report by **Claude Lillingston, B.A., M.D.**, *Gorleston-on-Sea.*

REPLY TO QUESTIONNAIRE WITH OBSERVATIONS.

1. Between 90 and 100 cases, including those in which attempts to induce a pneumothorax failed on account of adhesions. (Lest many of these cases be counted twice, it should be pointed out that most of them were in institutions from which independent returns are made. These institutions are: St. Mary's Hospital, London, Mundesley Sanatorium, Berks. and Bucks. Sanatorium, East Anglian and Maltings Farm Sanatorium, Nordrach-on-Dee, Banchory Sanatorium.) Cases were also in Nordrach-on-Mendip Sanatorium and Barrasford Sanatorium.

2. (*a*) Mainly unilateral disease which has thwarted proper institutional treatment for some months. Severe recurrent haemoptysis when there is little doubt as to the side of the chest from which the haemorrhage comes. In otherwise borderland cases, active laryngeal tuberculosis is an indication, for it often clears up promptly when the pulmonary disease is arrested by an artificial pneumothorax.
(*b*) Early disease of a benign character which reacts well to institutional treatment. Definite signs of intestinal tuberculosis. Diabetes. Ignorance of the medical attendant of each detail of the technique in particular and of the principles of the treatment in general. Active disease in both lungs; extensive but inactive disease in the better lung is no contra-indication. Moribund, cachectic cases not possessing even that small margin of vitality required to survive the initial discomforts of the operation. Age over 60. Marked mental instability. Bilateral renal tuberculosis.

3. Good if there is little or no active disease; otherwise bad.

4. In one case only, and that with disappointing results.

5. No case of sudden death, and only one of pleural reflex lasting about a couple of minutes. Surgical emphysema in several cases, with, in one case, slight dysphagia. Creation of an accidental pneumothorax by puncture of the visceral pleura in one case with no other ill effect than severe dyspnoea. Pleural effusion in about one-third of all the cases. Rupture

of a pyopneumothorax into the lung, followed by expectoration of much pus, and, in a few days, by death in one case. *Prevention*: After signs of pleural reflex had occurred at two refills in the above case, both hypodermic injections of morphine and local anaesthesia were prescribed at every refill, and no further signs of pleural reflex occurred. Surgical emphysema can largely be avoided by keeping the intra-pleural pressure low. The same precaution may possibly reduce the incidence of pleural effusion. But even in the case of such skilled operators as Professor Saugman, this complication seems to be very frequent, and it is doubtful whether it can be much reduced in frequency. Prevention of gas embolism and of pleural reflex can, on the other hand, be effected by meticulous attention to every detail, and the only unavoidable fatality is that which is due to gas embolism following the entry of inspired air, or gas already in the pleural cavity, into a ruptured or punctured blood-vessel. The relative importance of gas embolism and pleural reflex as causes of death has not yet been determined.

6. With strictly limited adhesions, notably adhesions confined to the apex of the lung, yes. Otherwise, no.

7. The apparatus should be as simple as possible. Saugman's needle is undoubtedly the best for inducing a pneumothorax. The same needle with a solid point and a side-opening close to the point is best for refills. Local anaesthesia supplemented by morphine hypodermically is indicated at the first few injections, and the local anaesthesia should be repeated at every refill of patients showing the slightest tendency to pleural reflex.

8. In more than half. This high proportion of failures is largely due to the fact that between 1910 and 1914 few patients in England were allowed by their medical attendants to try this treatment till the disease was in an advanced third stage.

9. Probably air is as satisfactory as any pure gas. The use of oxygen at the first injection may be theoretically advisable, but in practice, by giving a false sense of security, it may encourage operators to plunge about more freely with the needle than they would otherwise do, and thus the operation may actually become more dangerous for the use of oxygen.

10. Only from 200 to 500 c.cm. at the first injections. Yes: an injection of 1,200 c.cm. caused serious inconvenience in one case of almost complete pneumothorax. In some cases of embarrassed heart action and movable mediastinum, cautious regulation of the dosage of gas makes all the difference between brilliant success and utter failure. As a rule, small and frequent injections are better than large injections at long intervals, and in some cases it may not be advisable to exceed the atmospheric pressure. The operator should be guided far more by the intra-pleural *pressures* than by the *quantities* of gas injected. Ten years ago I thought nothing of creating an intra-pleural pressure of $+30$ cm. of water ; now for several years I have not exceeded a pressure of $+12$. Once only have I broken down extensive adhesions by a very high pressure, and I have not the vicarious courage to repeat the experiment.

11. I prefer a negative pressure at the end of the first two or three injections, as this indicates comparative freedom from adhesions. Later, when the lung is well collapsed, the pressure at the end of an injection should be determined by the needs of each case. With a large pneumothorax and movable mediastinum, the pressure should be only atmospheric, or one or two cm. of water above it. With a smaller pneumothorax and rigid mediastinum, a pressure of, say. $+6$ on inspiration and $+12$ on expiration may be the best.

12. This treatment gives better results than any other in a limited number of cases. The results depend not so much on a careful and experienced selection of cases, important though this preliminary consideration undoubtedly is, as on the care and skill of the physician in charge. This factor is so important that it is better for this treatment to be dispensed with altogether than for it to be taken up in a half-hearted, 'sloppy' manner. The differences in the results achieved at different institutions are almost completely to be explained by the differences in the skill and

conscientiousness of the physician in charge. When a visiting physician who has not mastered the technique of the operation delegates it to a house physician still more ignorant of the operation, it is inevitable that disaster must swiftly follow. Except in the most rare cases, the treatment should not be started in the patient's home ; it is essentially a treatment for institutions properly staffed. Every institution practising this treatment should be equipped with the X-rays.

7. Report by **Geoffrey Lucas, B.A., M.D.,** *late Medical Superintendent, Nordrach-on-Dee Sanatorium.*

REPLY TO QUESTIONNAIRE WITH OBSERVATIONS.

1. I have attempted artificial pneumothorax in 32 cases and succeeded in 24, with 8 failures. These figures refer to the past 8 years.

2. (*a*) The following is the type of case in which I consider artificial pneumothorax indicated. Cases of one-sided disease showing evidences of toxaemia and activity ; or cases in which the ' sound ' lung is only slightly affected and not the seat of *active* disease : cases which do not respond to sanatorium treatment persevered in for a period of three months, provided, of course, that the disease does not show signs of rapid progression, in which case I would not wait the three months.

   Cases in which haemorrhage persists and is uncontrolled by ordinary methods.

   Cases of persistent painful pleurisy with little, if any, evidence of intrapulmonary involvement.

   (*b*) The contra-indications are, in my opinion, only two. 1. When the patient is in a practically moribund condition. 2. When the patient is the subject of active disease in both lungs—the less affected lung being affected in more than one-third of its substance.

   In my experience of 24 established cases in only 2 has the procedure had any effect other than a beneficial one. In those cases where the treatment did not, for a time at any rate, stay the progress of the disease I have no hesitation in saying that life was prolonged and distressing symptoms, such as cough, excessive expectoration, fever, or sweating, were relieved.

3. In answer to this question I append views which I held and expressed in 1915, and have subsequently seen no occasion to change :

   ' It was formerly thought that by producing a pneumothorax in a bilateral case with quiescent limited disease on the " sound " side one ran a great risk of lighting up the disease afresh by throwing additional work on the " sound " side. This has not proved to be the case in practice. Indeed, if the pathological state of affairs is considered, it is seen that rather than exciting the disease to fresh activity one is in reality bringing about a condition of affairs which is conducive to arrest. When one lung is extensively involved and the other slightly so, a considerable amount of compensatory emphysema takes place in the " sound " lung. The alveoli are enlarged and the capillaries dilated ; subsequently the capillaries become thrombosed and atrophied, and *post mortem* the lung presents a swollen and anaemic appearance. Now when an artificial pneumothorax is produced the emphysematous lung is subjected to pressure, and consequently compression is brought to bear on the vessels and some obstruction to the circulation in that lung is produced. This in turn produces venous stasis, a condition which obtains, but to a much more marked degree, in the case of mitral stenosis. Thus there is produced in the " sound " lung the essentials aimed at in Bier's treatment of tuberculosis by passive hyperaemia, a condition of the lung which tends to bring about arrest rather than excitation of the disease.'

4. In only one case have I had an opportunity of attempting bilateral pneumothorax, and after collapsing one side I found it impossible on the other owing to pleural adhesions ; but if further opportunities were to occur I should have no hesitation whatever in employing this form of treatment, which I believe in certain cases to be sound.

5. I have experienced no accidents in any of my cases, and the only complication, of more than a transient nature, such as a slight degree of surgical emphysema, has been the appearance of pleural effusion, usually between the third and sixth month of treatment.

As to the avoidance of accidents, I again quote from my article in the *British Medical Journal* of 7th August 1915:

'With regard to the preparation of the patient for operation, when possible I prefer the patient to be at absolute rest in bed for two days previously. On the second evening an aperient is given, and, if the bowels have not acted satisfactorily, a simple enema is given early the following morning. The chest is then carefully examined, and three likely sites for puncture are chosen and painted with tincture of iodine to the size of half a crown. Three-quarters of an hour before the time appointed for operation 0·5 c.cm. of omnopon-scopolamine is given hypodermically. Half an hour later, if the patient is not well under the influence of the drug, a further dose of 0·25 to 0·5 c.cm. is given. This procedure is found most beneficial in diminishing reflex sensibility, whilst the rate and depth of respiration are not materially affected. The proposed site of operation is again painted with tincture of iodine and a hypodermic syringe containing 15 minims of a solution of novocaine and adrenalin is taken, and the needle plunged through the skin at right angles into the intercostal space. It is pushed onwards gently until it is judged to have reached the parietal pleura (this can often be felt by a sudden feeling of resistance to the needle). Two or three minims of the anaesthetic are next injected, and the needle is gradually withdrawn, injecting slowly the while. In this way a track is anaesthetized along which the Saugman's pneumothorax needle is subsequently passed. It is a practical point of some importance that no excess of anaesthetic fluid should be left immediately under the skin, as if it is there is a probability that the Saugman's needle may be blocked and the manometric oscillations consequently interfered with. For the same reason it is of great importance that the Saugman's needle should be absolutely dry, and for this purpose it is my practice to keep the needle in absolute alcohol until required for use. When taken out of the alcohol it is thoroughly dried over the flame of a spirit lamp, and hot air is blown through the needle by means of a small air-bellows attached to the proximal end. At the first operation I prefer to use a needle with an opening at the end, but when a potential space has been established between the parietal and visceral layers of pleura, I use a needle with a solid point and a lateral aperture at the end of the shank immediately above the point.

'With reference to the amount of nitrogen to be introduced and the alteration of intra-pleural pressure to be brought about at the first sitting, some diversity of opinion exists. The two principal factors governing this question are—firstly, the presence or absence of pleural adhesions, and, secondly, the size of the chest. A point to remember is that one can proceed more rapidly with safety on the right than on the left side of the chest, as the normal position of the heart is less interfered with by introducing gas into the right than the left pleural sac. The use of X-rays is of inestimable value in affording information as to the relative position of the intrathoracic organs, as percussion of the cardiac area becomes increasingly difficult and unreliable as the introduction of nitrogen proceeds. It has been my practice, in cases free from adhesions, to aim at producing a slight positive pressure (two to three cm. of water) at the third of three successive sittings, which have taken place at intervals of a day between each. I have found that in chests of average capacity three separate injections of about 500 c.cm. of nitrogen each will bring about this result.'

Warming of the nitrogen before introducing it into the pleural sac has, in my opinion, the effect of causing less shock and diminishing subsequent discomfort by avoiding to a considerable extent the subsequent expansion of the gas, which, if introduced cold, is warmed up to the body heat and so expands.

6. If I find only a small loculus it has not been my practice to attempt to break down adhesions by forcible pressure. But in one case, in which

I found a small pleural space, very material benefit accrued to the patient by keeping this comparatively small loculus filled.

7. The answer to this question is largely embodied in my answer to Question 5. I employ the apparatus recommended by Pearson and Lillingston as represented in Powell and Hartley's latest edition of *Diseases of the Lungs and Pleurae*.

   I always employ a local anaesthetic, both at the time of the initial operation and at subsequent ' refills '.

8. In 25 per cent.

9. I have no experience of any other gas than nitrogen, which has proved in my hands to be efficient.

10. Except where a pneumothorax is being induced for the purpose of controlling haemorrhage, I always gave a small initial quantity of gas, about 500 c.cm., but am guided by the constitutional effects and manometric readings. In one case with a free pleural space after 1,300 c.cm. of nitrogen had been given at a ' refill ' troublesome dyspnoea was experienced some 15 minutes later, due, I think, to the expansion of the gas. In another case where at a ' refill ' the pressure was raised higher than previously, an adhesion was unintentionally broken down, causing severe pain for some days.

    To my mind the quantity of gas given must be regulated solely by the sensations produced and by the manometric readings.

11. (a) This depends upon the side upon which one is operating. On the left side, on account of the proximity of the heart, I work more slowly. In a free pleural space I aim at obtaining a flat pressure (plus 0 minus 0) at my third operation.

    At the first operation I am content with reducing a normal pressure of minus 10 minus 6 to, say, minus 6 minus 3, watching of course the effect upon the patient.

    (b) Formerly I was in the habit of working with pressures as high as plus 12, but experience has taught me that a pressure of plus 4 is, in uncomplicated cases, quite sufficient to bring about the desired result, and since I have been content to work with lower pressures my results have been better and I have been struck by the fact that the patients are less prone to develop pleural effusion.

12. I am of opinion that in carefully chosen cases this form of treatment is of very great value and should be resorted to at an earlier stage of the disease than is customary at present. Too often valuable time is lost in waiting, and thereby, when the operation is resorted to, discredit is brought upon it through not producing more striking results. Too often cases are allowed to drift on month after month, when a pneumothorax, if successfully induced, would be of the greatest benefit. The delay causes a definite and progressive lowering of the resistance, so that when the operation is undertaken one is confronted with a much more serious state of affairs than need have been necessary.

8. Report by **W. Parry Morgan, M.A., M.D.,** *Cardiff*.

Dr. Parry Morgan writes : ' The questionnaire obviously refers to the treatment of one lung at a time and that by complete collapse. My work, all done before the War, was on different lines, so for statistical purposes it seems to me that my cases should not be dealt with in the reply, especially as the number was comparatively small and my technique not fully developed. However, I venture to think that the points raised in my last paper on the subject are of importance, and therefore enclose it for the Committee's consideration. In it I have suggested partial and, if necessary, simultaneous bilateral collapse as a method of treatment. Whether this will prove of such undoubted value as complete collapse I cannot say. On the other hand, I assert, most emphatically, that a single manometer apparatus is seriously defective and to insist on free oscillations before turning on the gas is wrong.'

The paper referred to by Dr. Parry Morgan is entitled ' Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis ', and was published in

On the questions raised by Dr. Parry Morgan the paper *in extenso* should be consulted. The conclusions arrived at are as follows :

1. Partial collapse of a tuberculous lung tends to give rest to any consolidated portion, and thereby to reduce auto-inoculation.

2. The changes which take place as a result of the absorption of gas tend to reduce the amount of strain in the diseased parts when this strain is compared with that which existed before collapse. A single operation for collapse is therefore likely to be followed by good results.

3. A moderate degree of collapse does not materially interfere with respiration provided it allows sufficient normal tissue to function.

4. Both lungs can be treated at one and the same time.

5. In all cases of aspiration of fluid from the pleural cavity, the fluid removed should be replaced to some extent by gas. This is desirable, in the case of tuberculosis of the lung, in order to give rest to the diseased parts, and, generally, because it prevents the valve action of the lung and all that distress which would result from attempts to empty the cavity completely.

6. The apparatus and method usually employed for the operation are seriously defective in many respects, and necessitate the puncture of the lung and leakage of air from it.

7. The defects can be remedied by the use of a slightly more elaborate apparatus.

Conclusions 6 and 7 express Dr. Parry Morgan's views in 1917. He desires now to modify them so as to read as follow :

6. 'A single manometer apparatus is seriously defective in many respects. The rule that "clean respiratory fluctuations" should be indicated by the manometer before gas is allowed to flow into the pleural cavity necessitates puncture of the lung and leakage of air from it.

7. ' The defects can be remedied by the use of a slightly more elaborate apparatus which includes a second manometer.'

9. Report by **S. Vere Pearson, M.D., M.R.C.P.,** *Senior Resident Physician,*
The Sanatorium, Mundesley, Norfolk.

REPLY TO QUESTIONNAIRE.

1. 64 (sixty-four).
2. (*a*) Progressive one-sided disease.
   (*b*) (i) Progress without artificial pneumothorax.
   (ii) Marked bilateral disease.
3. Sometimes beneficial ; sometimes none.
4. Never.
5. One death after (within an hour of) the initial injection : ascribed to pleural reflex.
   The procedure was adopted as a last resort in a case with bilateral disease after consultation with a London physician. The injection was given on the side with the least extensive lesion ; but on this side the lesion was supposed to be more active.
6. No, except when the adhesions are only partial and an effective pneumothorax can be produced compressing the lung where the most active disease is present. For example, of 64 patients treated here in the last ten and a half years, 21 had partial but effective (or temporarily effective) compression produced, while in the remainder (43) the pneumothorax was complete.
7. I believe in keeping the apparatus as simple as possible. I always employ a local anaesthetic for a first injection, and sometimes for a refill.
8. Sixteen per cent.
9. I usually use nitrogen.

10. My practice is not to give more than 400 c.cm. as an initial dose.

11. (*a*) This varies with the individual, as one finds variable pressures on first introducing the needle. (*b*) An average at the end of a refill is +3 and +7 cm. water.

12. It is a most valuable method of treatment.

Note.—For further opinions of mine please refer to my published articles on this subject :
1. Latham and English's *System of Treatment*, vol. i. (This article is written in conjunction with Dr. C. Lillingston.) 2. *The Tuberculosis Year Book*, vol. i. p. 150. J. Bale, Sons & Danielsson, 1914. 3. *The Lancet*, 15th July 1911. 4. *The Practitioner*, September 1911. 5. *The British Medical Journal*, 12th October 1912. 6. *The Lancet*, 26th July 1919.

10. Report by **Clive Riviere, M.D., F.R.C.P.,** *Physician City of London Hospital for Diseases of the Chest.*

Reply to Questionnaire.

1. About 80 cases—30 in private and about 50 in hospital practice.

2. Indicated in progressing or considerable disease—where the other lung allows it.

3. Quiet and localized disease generally bettered—otherwise harm.

4. No.

5. Never an immediate accident ; at most slight faintness. I have had pleurisies, mostly harmless. One perforation of lung.

6. Yes, often.

7. I consider movable bottles better than fixed. Always local anaesthetic for first few punctures.

8. I have not got out statistics up to date.

9. Air or nitrogen equally efficient.

10. Small. 300-400 c.cm. Have given 1,000 c.cm. for haemoptysis with no bad effect; but bad effects have been recorded.

11. (*a*) After initial operation a decided negative, as −5 mean pressure.
(*b*) No rule can be given—varies with case.

12. The method is of *enormous* value in *selected cases*. I have certainly saved many lives by it in advanced one-sided cases.

I have embodied much of my experience in my book *The Pneumothorax Treatment of Pulmonary Tuberculosis* (Oxford Medical Publications). The treatment should, in my experience, be kept in the hands of those specially trained in it (I have seen disastrous results from inexperience), and only used for carefully selected cases. Accidents during the operation are nearly always the result of bad methods; and the man who treats a very large number of cases in a short time is, in my opinion, extending the operation to many cases which would be better left alone. It is not a justifiable treatment for early cases, or for cases which can recover without it; on the other hand, it cannot be safely put off in cases which have got out of hand and do not progress otherwise—but the opposite lung must be a fairly good one.

I am sorry to be a little vague as to the numbers I have treated. My first 33 hospital cases were collected in a book, but after this the records went with their notes and I am thus uncertain as to the exact numbers.

11. Report by **Christopher Rolleston, M.A., M.D., M.R.C.P.,** *County Medical Officer of Health, Soke of Peterborough and County of Rutland.*

Reply to Questionnaire.

1. 41. In 12 no pneumothorax was produced owing to adhesions.

2. (*a*) Extensive unilateral disease in which no cure can be expected by ordinary methods of treatment. Less extensive disease in which prolonged rest fails to bring down temperature and other signs of constitutional disease are not improved.
(*b*) Advanced bilateral disease.

3. Provided there is no dislocation of the mediastinum—none.
4. No.
5. *Complications.* Subcutaneous emphysema, dislocation of the mediastinum; prevented by avoiding high pressures.
   Pleurisy in well over 50 per cent. No known method of prevention for this.
6. No.
7. Woodcock's apparatus is always very satisfactory and I use it. I use Clive Riviere's trocar and cannula in all operations. Novocain and ethyl chloride.
8. In 12 out of 41—29 per cent.
9. No.
10. Small; not more than 300 c.cm.
    Yes—pain, and, if large amount is persisted in, dislocation of the mediastinum with great dyspnoea.
11. (a) There is practically no alteration in pressure first noted before the gas is run in.
    (b) +3 to 4 on the Woodcock scale.
12. It is of the very greatest value.

Report on the Value of Artificial Pneumothorax.

There are cases of chronic pulmonary tuberculosis in which, no matter how long and how faithfully rest is applied, the disease progresses unchecked. For such cases pneumothorax treatment produces eminently satisfactory results. This treatment was first started in Peterborough on 6th December 1916, and now forms a very considerable part of the work of the Tuberculosis Officer. The operation has been tried on 38 patients since 1916. In nine of these 38 the treatment was impossible owing to obliteration of the pleural space from adhesions. After three or four attempts the treatment had to be abandoned. In 12 others this measure failed. In four the procedure was given up at the patient's own request, in three instances after a very imperfect trial, only one or two injections of gas being allowed. In one, influenzal pneumonia set in, involving the other lung, and death rapidly ensued just when the patient was beginning to benefit. In another an empyema in the pleural cavity led to a fatal result. In a third pleurisy supervened and prevented the further injections of gas, adhesions being formed as the fluid was absorbed. In a fourth the disease spread to the larynx and to the peritoneum. In four others the disease spread to the other lung. All these 21 unsuccessful cases were of great severity. Seventeen of them are now dead, three are worse, and in one the condition is unchanged.

At the present time there are 16 patients under treatment, and one who had nearly completed her cure had to leave the city of Peterborough for that of Chester. I append brief notes on these 17 cases:

1. Z. B. An artificial pneumothorax was established on 6th December 1916, and the treatment was continued in Peterborough up till April, 1919, by which time tubercle bacilli had disappeared from her phlegm. She has gained two stone in weight. As her husband left to take up work and live in Chester her treatment has had to be continued in Liverpool. In a letter dated 31st October 1920, Dr. Crane, of Liverpool, writes: 'Mrs. W. had her last refill seven weeks ago. She has no cough and no sputum, and there was no sign of activity in the lungs.'

2. L. J. H. was first seen on 1st August 1917, and proved a very severe case of bilateral disease with a high swinging temperature and rapid pulse. Rest in bed failed to produce any improvement in the constitutional symptoms, although the physical signs in the right and better lung diminished. Artificial pneumothorax was performed for the first time on 3rd October 1917, on the left side, and since that time, with the exception of an attack of pleurisy with exudation, which did not require tapping, the progress has been continuous. His temperature is normal; his pulse slow. There is only a little sputum containing no tubercle bacilli. He is able to do a fair amount of work.

3. O. B. First seen on 16th May 1917. She gave a history of severe haemoptysis. She presented signs of cavitation in the left upper lobe, and crepitations at the right apex. She gradually got worse. The disease spread throughout the left lung. Her pulse became more rapid and her temperature higher. An artificial pneumothorax was induced on 7th November 1917, and has been continued up to the present, at the end of December 1920; her general condition is good. She has a little cough and phlegm, but there are no tubercle bacilli in the sputum. She is able to do a fair amount of home work. I am of opinion these three cases have been observed long enough to say that they have derived enormous benefit, and that by no other treatment would their lives have been preserved.

4. T. A. Disease began in 1917, but as the patient was in the army no treatment could be started till 1919, when the disease had spread considerably, cavitation being marked in the right upper lobe, whilst he could hardly speak from laryngitis. Artificial pneumothorax was performed on 25th April 1919. Early in October 1919 crepitations occurred all over the left lung and he was very ill. On 29th October the temperature had fallen. Fluid was definitely diagnosed on the right side on 12th November 1919, and there was much displacement of the heart to the eighth left space. Now only 350 c.cm. of gas were needed to produce a pressure of up to $+4$ $+5$ on the Woodcock scale. He remained fairly well till October 1920, when he had an attack of pleurisy on the left side which cleared up in much the same way. His general condition is pretty good, but there is evidence of bilateral disease and there are still tubercle bacilli in the sputum. On the other hand, the condition of his larynx is perfectly satisfactory.

5. T. Y. First seen 8th February 1919. Disease began with pleurisy in February 1918. He gradually lost strength and went to a military hospital in October 1918. On examination there was dullness and crepitation over the whole of the left lung, with blowing breathing at the apex. Tubercle bacilli were present in the sputum. His weight decreased from 9 st. to 8 st. 10 lb. An artificial pneumothorax was induced on 11th June 1919. Treatment was uneventful. He is now in excellent health, has no cough or phlegm, and is able to work on a small holding.

6. Q. X. First seen 26th May, 1915. She had been ill, on and off, with cough since 1912. On first examination she was considered to be fit for work, as her general health was good, and there was only an inactive cavity at the right apex. She remained well till May 1918, when she was attacked with much cough and sputum, and was intermittently febrile. The signs on the right gradually increased in extent till, in February 1919, the whole of the right lung was involved. On X-ray examination dense infiltration was observed throughout the right lung. A successful artificial pneumothorax was induced on 15th March 1919. On 26th March 1919 the temperature was normal and the appetite good. On 7th April 1919 complaint was first made of dyspnoea, and by the middle of April 1919 the breathing was stertorous. The heart was displaced, the apex being in the anterior axillary line. Things went on fairly well till August 1919, when there were abundant frothy expectoration and violent attacks of suffocating cough. In September the amount of gas required to produce a moderate positive pressure varied between 200 and 300 c.cm., or less than half the previous amount. In October 1919 fluid was noted on the X-ray screen examination, extending as high as the inferior angle of the right scapula. In January 1920 the fluid had much increased, and 1,800 c.cm. of straw-coloured fluid were removed and replaced by an equal quantity of nitrogen gas. She improved after this and began to put on flesh, but the amount of gas which is now introduced at an interval of 14 days varies between 150 and 200 c.cm. There is slight expansion of the lung at the right apex. There is no cough and no phlegm. Her appetite is good and she can do a considerable amount of work.

The case illustrates the discomfort produced by the onset of pleurisy with effusion of fluid and the difficulty of its detection if X-rays are not available.

7. X. P., aged 13. Was first seen in July 1918. She gave a history of ill health, cough, and phlegm for nearly a year. There was a mass of glands the size of a Brazil nut under the right sternomastoid muscle. Her temperature

was 99° and her pulse 120. There was a cavity at the right apex and infiltration down to the third rib. On X-ray examination there was dense infiltration throughout the right lung. She went on without any marked change till May 1919, when the glands broke down and had to be incised. On 23rd July 1919 an artificial pneumothorax was induced and has been continued up to the present time. Her general condition is most satisfactory. Her pulse is slow. There has, however, been no increase in weight. The glands in the neck have now subsided.

The remaining ten cases have not been long enough under treatment to justify a detailed account. All, however, have, without exception, improved, and in two a cure may be confidently expected. Two will almost certainly go to the bad. In considering the results of pneumothorax therapy it should be remembered that only third-stage cases have been submitted to this form of treatment. Such lives are greatly prolonged, and as they cease to expectorate they are no longer a danger to others. This form of treatment is gradually extending throughout Great Britain, but its adoption entails an enormous amount of work. Should it become general it will mean in areas other than this county a large increase in the professional staff of all institutions. Each operation takes about half an hour, and each case has to be operated on for $3\frac{1}{2}$ to 4 years. Recently, in Norway and other continental countries, those cases in which there is obliteration of the pleural cavity by adhesions have been treated by excision of all the ribs on the affected side. Excellent results are reported, but it is difficult to find a surgeon in this country to undertake the work.

Reference.

See also 'Artificial Pneumothorax Treatment of Pulmonary Tuberculosis in County Areas'. By Christopher Rolleston, M.A., M.D. *Medical Press,* 12th June 1918.

12. Report by **D. P. Sutherland, M.B.,** *Tuberculosis Officer, City of Manchester.*

Reply to Questionnaire.

1. 27.
2. (*a*) Cases are taken generally where the disease is more marked upon or limited to one side. If the appearance and condition generally show no material improvement under sanatorium treatment, pneumothorax should be considered. An X-ray examination always supplements the clinical findings.

   (*b*) Extensive bilateral disease, embarrassment of the circulation, extensive bronchitis and emphysema, and any serious debilitating illness.
3. A certain amount of compensatory emphysema probably occurs in the opposite lung, and certainly the breath-sounds approximate to a more puerile type. Even where slight disease exists I have only found the signs to be increased in one instance.
4. No.
5. Simple pleural effusion has occurred in two cases. No cases of severe shock. No cases of septic trouble. In one patient acute pain in the neck and arm in the injected side was complained of during the course of injection. This passed off in five minutes' time, although a great deal of distress was caused whilst it lasted. This was an old case who had been having injections for some considerable time, and the reason for this complication was not obvious. See also under 7.
6. Not if these adhesions prevent collapse to a material extent.
7. The technique is that of a surgical operation. All cases are commenced in a sanatorium and not in an out-patient department. This I consider a very important matter. The simpler the apparatus the better. The essential points are an apparatus which is easy to keep clean and simple to work. It should not allow too rapid filling of the chest nor permit of a greater pressure than the equivalent of about 6 or 7 centimetres of water. A platinum needle is preferable to a steel one and there must be an easy release for the gas if required. Local anaesthesia is always used and very carefully given. Injections themselves should be quite painless. The full confidence of the patient must be secured.

F

8. Records not kept ; perhaps failure has occurred in six cases, but possibly in more.

9. No. Either nitrogen or air—filtered.

10. The first injection is generally only about 150 to 200 c.cm. of gas. It is stopped when the general condition of the patient appears to demand it, that is, if the pulse-rate begins to be increased or if there be pain, dyspnoea, anxiety, or sweating. It matters very little whether positive pressure is obtained or not at this injection.

11. (a) See 10.

(b) This again is largely judged by the condition of the patient, but a positive pressure of any amount, if maintained whilst the manometer is alone connected to the pleural cavity, is adequate. In a general way 3 to 5 centimetres of water-pressure is registered. Of course, even with the manometer at zero, the lung will be as collapsed as it is possible to obtain it. High pressures simply distress the patient for a short time and are apparently relieved by rapid absorption.

12. My opinion is that pneumothorax has a definite rôle in the treatment of tuberculosis, but that its scope is limited in this as in all the other special methods. Each individual case is to be carefully considered upon its merits.

I annex a table which summarizes the results of 21 cases treated by me.

Results of First Treatment, Domiciliary, Dispensary, and Sanatorium.

Stage of Disease.	No. of Cases.	Working Capacity.	Tubercle Bacilli.
I.	1	Fair.	Present.
,,	1	Nil.	,,
II.	8	,,	..
,,	2	Very light.	,,
III.	4	Nil.	,,
,,	1	Fair.	,,
I.	1	Impaired.	Not found.
II.	3	Nil.	,, ,,
All stages.	21 cases.	In 17 tubercle bacilli were present ; in 4 tubercle bacilli were absent.	

Final Results after Pneumothorax (January 1920).

Stage of Disease.	No. of Cases.	Working Capacity.	Tubercle Bacilli.
I.	2	Full.	Not found.
II.	5	,,	,, ,,
,,	1	Full to October 1818, then removed and lost sight of.	,, ,,
,,	1	Fair, then killed in accident.	,, ..
,,	1	Fair.	,, ,,
,,	1	,,	Present (few numbers).
,,	1	Good to leaving Manchester. Died August 1918.	Not found.
III.	1	Full.	,, ,,
,,	1	Fair.	,, ,,
,,	2	Nil.	Present.
,,	1	Nil. Died December 1919 of tuberculous meningitis.	,,
I.	1	Full.	Not found.
II.	2	,,	,, ..
,,	1	60 per cent.	.. ..
All stages.	21 cases.	In 4 tubercle bacilli were present ; in 17 tubercle bacilli were absent.	

13. Report by **Norman Tattersall**, **M.D.**

Tuberculosis Physician, Welsh National Memorial Association.

Reply to Questionnaire and Observations.

1. Treatment was attempted in 37 cases : 26 were treated ; in 9 there was failure to induce an artificial pneumothorax and in 2 treatment was started but discontinued for various reasons.

2. (a) *Indications for treatment.* 1. Progressive disease not responding to the usual lines of treatment should always call for the consideration of the possibility of utilizing artificial pneumothorax. Activity is more important than extent or locality. 2. Recurrent severe haemoptysis.
   3. Severe pleural pain. }
   4. Persistent cough.   } In some cases, other things being equal.
   Occasionally good results are obtained in apparently hopeless cases, but my feeling is towards greater conservatism, which amounts to coming to a decision as to the prognosis earlier than I used to do, and instead of going on *hoping* for results from rest, &c., *getting* them by artificial pneumo-thorax.
   (b) *Contra-indications.* 1. *Age.* Over 45 needs very careful considera-tion. 2. *The state of the other lung.* Definite activity, especially hilus spread. 3. *Acute pneumonic type of disease.* 4. *Complications.* Kidney and intestine.
   Social position of patient. This has to be taken into consideration ; I have found that my own results are very definitely better in patients who through their social position can take a more prolonged period of rest and treatment before being compelled to return to work, so that one must exercise greater conservatism with the worker than with those in better social circumstances.

3. *Effect on other lung.* In suitable cases no adverse effect has been observed. There must be some compensatory emphysema, but this is usually not obvious unless pleurisy in the pneumothorax has led to marked con-traction of the chest on that side. An apparently arrested lesion in the other lung may become active in one to two years, but I do not find that the production of pneumothorax on the other side makes this more likely to occur than if a pneumothorax had not been induced. An active lesion in the other lung will usually progress more rapidly, but in those cases a pneumothorax should not have been induced.

4. *Pneumothorax induced on both sides.* I have done a bilateral pneumo-thorax in two cases. In one case this was done because after 2½ years of freedom from symptoms disease became active in the other lung. I tried partial compression of the newly active side with suspending of refills on the other side for some months. The original side expanded and became active. No benefit was obtained. In the other case I tried a partial double pneumothorax as suggested by Dr. Parry Morgan. Only very temporary improvement was obtained, but I consider that in this case the disease was already too far advanced on both sides for it to have been at all suitable for pneumothorax treatment.

5. *Accidents or complications.* 1. *Subcutaneous emphysema* has occurred fairly frequently, but never to such an extent as to cause worry or discomfort. To diminish it I advise patients to press firmly with the hand over the site of the puncture whilst coughing, and to restrain coughing as much as possible.
   2. *Mediastinal emphysema* has occurred in two cases, causing a sense of constriction and slight dysphagia. Both these were cases with marked adhesions. The discomfort was only temporary and did not recur when high pressures were avoided.
   3. *Vomiting after the operation* has occurred in several cases, but never since I have given up the use of a preliminary injection of morphia.
   4. *Pleural effusion* has occurred in 38 per cent. of cases. In three cases it has led to complete obliteration of the pneumothorax cavity and cessation of treatment. In one of these three cases the ultimate result was very

good as apparently dense fibrosis of the lung occurred simultaneously. To avoid it the most strict attention should be paid to asepsis. I also am forming the opinion that the frequency of pleurisy is increased by patients (although with a normal temperature) being allowed too much exercise in the early stages.

5. *Rupture of lung* occurred in one case, causing a spontaneous pneumothorax and very great dyspnoea. The pressure was relieved three times by aspirating air, and although a pleural effusion developed this did not become purulent and the ultimate result was very good.

6. *Pleural shock* has not occurred in my experience.

6. *Results in cases with adhesions.* These are not so good as in cases where a complete pneumothorax is obtained, but are quite good enough to justify keeping up the treatment. The results in 10 of these cases are as follows: Well and at work, two (20 per cent.); much improved, two (20 per cent.); improved, three (30 per cent.); dead, three (30 per cent.). The difference between these results and the whole series is as follows: *All cases* (including those with adhesions), well and at work in 1–3 years = 35 per cent. *Complete cases only*, well and at work in 1–3 years = 44 per cent.

7. 1. *Technique.* The most strict asepsis should be observed. The amount of gas should be small, and refills often repeated, except in cases of haemoptysis. I prefer a trocar type of needle for induction.

2. *Apparatus.* The simpler the better. I find that the two-bottle type (Pearson and Lillingston) is perfectly satisfactory.

3. *Anaesthesia.* I have given up the use of a preliminary injection of morphia. On every occasion I use a local anaesthetic, and for the last two years have used a preparation of Messrs. Parke Davies called 'Locasthetic', which contains 0·75 per cent. cocaine with adrenalin. I have occasionally used as much as three or four c.cm. and have never observed any ill effects.

8. *Failure to induce pneumothorax* has occurred in 24 per cent. of the cases I have attempted.

9. *Choice of gas.* I do not consider this important if the greatest care is used in observing the manometer, and never disregarding a warning. I have used air only for the last three years and I find the results as good as when I used nitrogen.

10. *Quantity of gas.* This should be small except in cases of haemoptysis. I have not observed any ill effect from using a large amount (over 1,000 c.cm.) except temporary dyspnoea and some giddiness.

11. *Pressures* vary within very wide limits both after the initial operation and after complete collapse. This is especially the case when adhesions are present. (*a*) After initial operation −10 to −2 c.cm. water. (*b*) After complete collapse +4 to +9 c.cm. water.
The lowest pressure possible to obtain complete collapse should be used, and each case has its optimum pressure. If there has been pleurisy the pressure is always higher.

12. The results speak for themselves and prove the immense value of treatment. In my own 26 cases which have been completely treated the prognosis in every one previous to treatment was hopeless. The results, after one to four years, and in two cases eight years, are as follows: Well and at work, 35 per cent.; improved (some probably only temporary), 32 per cent.; dead or dying, 33 per cent.

Further General Remarks.

Social position. This has already been mentioned earlier in the report, but is a matter on which I feel strongly.

Choice of case. I believe that time will show that the treatment will be adopted more early in the course of the disease than has been the case in the past. It should not be reserved as a last resort for hopeless bilateral cases, but every effort must be made to determine the ultimate prognosis on ordinary treatment as early as possible.

X-ray control. All my cases have been done without having an X-ray plant at the hospital. In a number of the cases I have been able to take the patients to a hospital some distance away, where I have had the benefit of X-ray control. An X-ray plant will shortly be installed for my own use, and, although I believe that X-ray control is essential to one's peace of mind, it is my experience that with due clinical care the absence of X-rays should not be an absolute deterrent to any one who will exercise great caution.

Pleurisy and pleural effusion. I have noticed that in a number of cases in which I had successfully got the disease under control by pneumothorax treatment and had transferred the patients to a sanatorium, where, in addition to the continuation of their refills, they underwent graduated exercise, the percentage of cases which developed pleurisy was greater than those who did not go to a sanatorium and thus spent more time at rest. Other observers have expressed the opinion that rest should be maintained for a long time after the induction of a pneumothorax, and in the light of my experience I believe that this is correct.

14. Report by **Jane Walker, M.D. Brux.,** *East Anglian Sanatorium.*

Reply to Questionnaire.

1. 114.
2. (*a*) Extensive mischief in one lung causing general toxaemia.
   (*b*) 1. If more than one lobe of other lung involved. 2. If albuminuria present. 3. If patient of very nervous temperament.
3. It varies with case.
4. No, but have seen it done at the same time in Italy.
5. None, except occasional puncture of a vein.
6. No.
7. We use the simplest apparatus possible and have found it so satisfactory that we have never seen any reason to change it.
   Yes, novocain or Locasthetic.
8. 10·5 per cent. (i.e. 12 out of 114).
9. We have used nitrogen, and lately always air.
10. Small.
    Yes, breathlessness and some digestive disturbance.
11. (*a*) Usually still negative.
    (*b*) +10 + 14.
12. It alleviates symptoms and prolongs life. Our practice has been to use it in advanced cases in whom there was little prospect of recovery; consequently our percentage of 'cures' has been small.

15. Report by **R. C. Wingfield, M.B., M.R.C.P.,** *Medical Superintendent, the Brompton Hospital Sanatorium, Frimley.*

Reply to Questionnaire.

1. Forty-one.
2. (*a*) 1. For haemoptysis when not controllable by the ordinary means, in cases where there is a fair certainty from which lung the blood is coming. 2. In cases of patients who bring up large quantities of blood at intervals of a few weeks or months, when it is certain that these haemoptyses are likely to recur, and when there is a fair certainty which lung is in fault, and if the disease is mainly one-sided. 3. Those cases in which the disease is mainly *one-sided* and who have not responded to ordinary methods of treatment.
   (*b*) Marked bilateral disease.
3. I have not been able to detect any evil effect on the other lung, save occasional pleurisy over the lower lobe.
4. No.

5. One case of sudden loss of consciousness with subsequent death, due presumably to 'pleural shock', as no air was introduced and the needle at the time was fitted with an accurately fitting stylet.

One case of haemoptysis due to puncture of lung.

I am of opinion that if the details of technique as set forth in *Artificial Pneumothorax Treatment*, by Dr. Clive Riviere, are followed *conscientiously*, all accidents should be avoided.

6. No. Moderate to bad.

7. My technique is practically that of Dr. Clive Riviere as set forth in his book. I have found the type of apparatus illustrated in Powell and Hartley's *Diseases of the Lungs* and the Parry Morgan apparatus equally good.

I employ a local anaesthetic in each case and regard its use as very important.

8 Twelve per cent.

9. No. I used to use oxygen for initial inductions and nitrogen subsequently. For three or four years I have used ordinary air and find it just as good.

10. The amount of gas used at the first induction or at any subsequent refill is absolutely unimportant. The important point is the amount of change of intrathoracic pressure. Until complete collapse or sufficient collapse has been obtained the pressure should not be altered by more than two to three centimetres of water.

I have never observed bad effects from large quantities of gas given on initial inductions, but have observed them in cases of too rapid alteration of pressure.

11. (*a*) A pressure of one to three centimetres of water above the intra-thoracic pressure recorded at the initial puncture.

(*b*) Anything from two centimetres of water to twenty centimetres of water.

I consider it important to be guided by the mean pressure at any moment, as the excursion of the manometer depends upon the rigidity of the rubber tubing and the calibre of the needle in the chest.

12. With careful selection of cases following the rules in answer to Question 1, I consider the treatment a very valuable one.

16. Report by H. de Carle **Woodcock, M.D., F.R.C.P.E., D.P.H.,**
Chief Clinical Tuberculosis Officer, Leeds.

REPLY TO QUESTIONNAIRE AND OBSERVATIONS.[1]

1. Probably 500. A large number of records were destroyed by fire.

2. (*a*) *Indications for the Operation.*

(1) Early cases in which the disease is showing a continuance of destructive progress. By early cases I mean cases in which the physical signs and the signs on X-ray examination point to concentrated disease of one apex or diffuse disease in one lobe, and in which the symptoms of toxaemia are slight.

(2) Cases in which the disease is advanced but unilateral. Cases where cavitation is marked, though the disease is localized. These should always, if possible, be treated by artificial pneumothorax. This is especially necessary when there is much toxaemia, the result of absorption of purulent excretion—a secretion following excretion.

(3) Cases still more advanced, but in which there is enough lung on either side to carry on the pulmonary function. This last class does not admit of a closer definition because the tolerance for interference by artificial pneumothorax varies in every individual and is not a fixed quantity. Shock is most easily induced in some patients, whatever the stage and whatever the amount of disease. This tendency to shock cannot, as far as I know, be accurately anticipated, though one gets an instinct for the patient with whom one has to work with intense caution. Speaking

[1] See also '5. Report by Dr. Z. P. Fernandez', p. 68.

generally, a North country man bears the operation with less shock than a South country man. The imaginative man is a poor patient at the beginning, but the best possible patient at the end when the operation has been successful.

(4) Cases of profuse haemoptysis. Here *the* remedy is artificial pneumo-thorax, if you know where the blood is coming from, and if the amount of working lung is sufficient to carry on and sustain life after artificial pneumothorax has been done. (*Note.*—When in doubt as to the position of the bleeding vessel, and especially if the case is a desperate one, it is wise to consider that the blood is coming from the lung which is most diseased, and in which the disease is most chronic, and not, as I at first thought, from the lung which shows the most recent and presumably the most acute disease.)

In all these cases it must be presumed that there is an open pleura, or, if adhesions are present, that there are pockets of open pleura sufficiently large to allow of extensive compression of the lung, or to permit, in addition, of the vascular reactions which may result in beneficial auto-intoxication.

(5) Cases in which the mediastinal barriers are not too rigid. (*a*) Bronchiectasis. (*b*) Pleurisy with effusion, including serous, purulent, and encysted effusion of the interlobe, especially with vomica. (*c*) Acute pleurisy. (*d*) Pneumonia (lobar).

These cases give themselves to artificial pneumothorax if the conditions already mentioned are met. Pneumonia, however, requires a special note.

(*b*) Contra-indications.

Artificial pneumothorax must be avoided in the following cases:

(1) Cases of chronic interstitial nephritis, especially with high blood-pressure, tendency to so-called cardiac asthma, and oedema of the larynx. These cases of interstitial nephritis must not be confused with those cases of albuminuria where albumin is an index of injury to the cells of the tubules owing to excretion of tubercle through the kidney.

(2) Cases of myocarditis, degenerative and not due merely to toxaemia or to exhaustion from pulmonary suppuration.

(3) Cases where true asthma is present in addition to pulmonary tuberculosis.

(4) Cases of very marked bilateral emphysema with evident distress on exertion.

(5) Cases of diffuse purulent bronchitis; that is, cases in which the bronchial tree is pathological rather than the alveoli.

(6) Cases with complete symphysis pleurae.

(7) Cases of hilus and peribronchial disease in which the lung has not been subjected to ulceration.

(8) Cases in which you can only find a pleural pocket in the vicinity of large vessels, or in which the collateral circulation on the surface of the lung is enormously exaggerated.

(In these latter cases there is, I think, a danger, not only of gas embolism, but also of solid embolism from débris plugs, if these are disturbed.)

(9) Laryngeal tuberculosis associated with pulmonary disease too extensive to allow of pulmonary functioning after operation. It should be noted, however, that laryngeal tuberculosis, due in most cases to fouling of the laryngeal mucous membrane by floods of pus, is often relieved when these floods of pus cease.

(10) Presence of auricular fibrillation.

(11) Tendency to pleural or pulmonary reflex; the first showing itself as an extreme liability to syncope, possibly followed by convulsions: and the second as an extreme tendency to acute pulmonary oedema.

(12) Bilateral and extensive miliary tubercle, even if the physical signs are indefinite or slight, the symptoms being the decisive factor.

(13) Concomitant intestinal tuberculosis of considerable extent, especially if accompanied by diarrhoea.

(14) Clinically, cases associated with foetid sputum; these have not done well, and therefore, other things being equal, they have been excluded.

(15) Cases of arrested disease. These should never be interfered with, even if the signs are marked.

3. *Effect on other lung.* Almost always a pneumothorax which lessens the daily amount of purulent sputum benefits both lungs, pulmonary tuberculosis being almost invariably bilateral. If disease is present only in one lung, pneumothorax in the affected lung protects the sound one by diminishing the risk of infection. In very rapid cases of acute tuberculous pneumonia, probably due to infection by the blood-stream rather than by the lymphatics (see Cobbett's experiments), I have thought that artificial pneumothorax in two cases has excited the early appearance of disease in the second lung. Pleurisy is so common in pulmonary tuberculosis that the appearance of this complication affecting the lung not operated on cannot be taken as an indication that artificial pneumothorax has caused the spread from one lung to the other. In the cases that I have suspected the pleurisy was basal, was of acute onset, and was followed by rapid destruction of the lung with cavitation.

4 *Pneumothorax on both sides.* Yes, often. There are four cases under treatment now. All are advanced, and the results are not happy. One patient is dying now. Another died two weeks ago.

5. *Accidents and complications.* Shock has been the most common. I avoid this by giving the first time what I shall call a preliminary operation, in which I go through all the steps of the operation without actually introducing gas; or if the patient shows great nervousness I even content myself with the induction of local anaesthesia alone. Patients who have for a long time been kept in a recumbent position must not be allowed to assume the perpendicular position just previous to the operation. Nor must the patient who is about to be operated on have his imagination excited by seeing another patient operated on, by hearing groans, or in any other way. Neglect of these precautions has increased the tendency to shock. Care must be taken to cause as little pain as possible; local anaesthesia is absolutely essential. Never inject quinuria into the deeper tissues; and never inject anything with force. Morphia should not be given before the operation; it has increased shock in several cases, the patient having been alarmed by nausea. But it should always be given *after* the operation if there is severe pain; in these cases it never causes nausea, and in relieving pain it relieves shock. Pain in pneumothorax, especially if it occurs during the first operation, always causes a certain amount of shock, and this is sometimes out of all proportion to the pain caused.

(1) If *shock* does take place (the signs of severe shock being a rapid, feeble heart, rapid breathing, acute oedema of the lung, much as in a very severe attack of asthma, unconsciousness, dilatation of the pupils, epileptiform convulsions, and possibly squint): in the few cases that I have met with the treatment that has been successful has been artificial respiration; massage of the heart by pressing the diaphragm up, pushing the fingers under the ribs; pulling forward the tongue; administering oxygen by a tube through the nostrils; and the administration of pituitary extract; the object of all this being to overcome the sudden and very dangerous ventricular dilatation.

(2) *Gas embolism.* I have not met with a case of gas embolism of the tragic kind described by Brauer and by Saugman, but I have had one case in which hemiparesis followed the injection of a few c.cm. of gas (nitrogen). The hemiparesis was only discovered the next day; it was slight. The patient was in an advanced condition (bilateral disease). I was not certain that it was a case of gas embolism, but thought from the delayed symptoms that it was an embolism from a small amount of solid débris. I believe that many cases of so-called gas embolism are cases of shock, i.e. combined pleural and pulmonary reflex. To prevent gas embolism the needle should be inserted away from the root of the lung; I prefer the mid-axillary position in a line with the nipple. The needle should not be a long one and should be introduced cautiously, so that immediately there is a manometric negative indication the needle should be pushed no farther. Gas embolism is obviously likely to occur

when the venous plexuses of collateral circulation are present and are injured; or when a vein is canalized, whether a vein of the plexus or a deeper pulmonary vessel. The obvious remedy for gas embolism is to use a suction syringe whenever the circulation of the lung and pleura is presumed to be abnormal. The suction syringe detects the presence of blood in the needle. A glass interception chamber filled with cotton wool (the chamber lying along the course of the tube) also serves to indicate blood if this regurgitates into the interception chamber.

Clark—one of my colleagues—always passed the stilette down the needle, and if on withdrawal this showed blood-stains, he drew out the needle and chose another spot. If then it is suspected that a vessel has been canalized or torn, gas must not be passed through the needle.

I use a stout hypodermic needle to introduce the gas, and I have given up both Lister's and Saugman's pattern. The hypodermic needle causes the minimum of injury; it must be about 1 cm. longer than the ordinary.

(3) *Deep and superficial surgical emphysema. Deep emphysema* is the dangerous kind, travelling along the oesophagus or trachea into the neck; it may cause great distress, and where the patient is already very ill may hasten his death. It has been due in my cases to the use of too high a pressure and putting in too large a quantity of gas. It is most likely to occur in a first operation before you have learnt to know your patient. The pressure which will cause a splitting of the pleural capsule (a sort of false passage) may not be a very high pressure, but it has been too high for the patient's tissues.

Superficial emphysema has seemed to me to be a return flow of gas along the track of the needle. Its signs are well known, and it is prevented by tight strapping after the operation, over the site of puncture.

(4) *Asphyxia.* In cases of ordinary emphysema a very small pneumothorax may bring about a remarkable change in the patient's condition. *Cyanosis* with symptoms comparable to those of strangulation may occur. I have seen one case. An emphysematous lung is very readily disturbed.

(5) *Bleeding.* A fatal haemoptysis may follow the clumsy manipulation of the needle. I have not seen such a case, but I have heard of one. I have on one occasion seen a slight haemoptysis (about a drachm of blood) follow an operation performed apparently with care. The remedy is to watch the manometer for a negative rise and not to push the needle too deeply. A hypodermic needle such as I use is not likely to cause this accident. In 'bleeders' or in patients—and there are such—with a congested granulation-covered pleura, it is wise to give calcium chloride for several days previous to the operation.

(6) *Perforation of a diseased lung area,* thus causing a pneumothorax similar to the natural pneumothorax, we know too well. I have not met with such a case, but Saugman mentions one where this accident appeared to have occurred. This accident is prevented by never putting the needle through any area save one that is resonant. I never, under any circumstances, try to force gas into the pleura in the very central point of the diseased lung; I rather make for the periphery of the disease.

(7) *Acute pleurisy.* I have several times seen acute pleurisy, in one case of a most violent character, follow an induction of artificial pneumothorax. I am sure that morphia aborts such an attack and should always be given where there is pain after the operation. Pain may not immediately follow the operation: it may come on in an intense fashion several hours afterwards. One is more likely to get it after a small injection of gas than after a large injection. I have seen an acute pleurisy follow what I have described as a preliminary operation (see previous note). There should be no operation if the patient is suffering from a so-called 'influenza'; I have thought in one case that this was a febrile pleurisy and that the operation had stirred it into acute activity.

6. Yes. Most of my operations have been in the presence of adhesions. The only difficulty has been due to the fact that in such cases the mano-

metric reading sometimes leaves one in doubt as to the position of the needle-point. In the presence of adhesions you may get readings which leave you in doubt whether you are (1) outside the pleural sac, (2) inside the pleural sac, and (3) in the lung.

(I shall refer to this in another publication.)

7. I use *novocain* 1 per cent. and give plenty, 3 c.cm. at least. I have not seen any harm from double that quantity. The novocain must be freshly made. I have seen symptoms, indistinguishable from shock, due apparently to the use of old and therefore poisonous novocain.

At the London International Congress, 1913, I published notes of two cases of artificial pneumothorax with injections of *paraffin* into the pleura. I discussed with Professor Saugman the probable value of this treatment, and we decided that it was worth while proceeding with it. Since then I have continued this mode of treatment with the object of separating the layers of the pleura, of causing partial compression of the diseased lung, and of assisting the later fibrosis, which is, indeed, the one aim of all our treatment. My first hope was that the paraffin injection would prevent the necessity for the operation of thoracoplasty or decostalization. The paraffin I use is of the ordinary medicinal kind. I am thinking of using, in suitable cases, a form less liquid and more capable of becoming solid at body temperature.

Another method of treatment is to apply weights to the side where there is most disease. I have only been doing this for a few months and cannot yet report as to its value. I am arranging for pneumatic pressure.

Urea-hydrochloride and quinine. This can be used and is used by me together with novocain in the same quantity and strength. It must only be injected superficially and it must be injected slowly. The injection must be subcutaneous and not intradermal ; the latter causes sloughing.

Apparatus. I use an apparatus similar to the one used by Vere Pearson, made for me by Messrs. Reynolds and Branson, of Leeds, with my own special manometer and the Parry Morgan throttle. Two manometers, therefore, are used. I would not on any account go back to the single manometer.

8. Here I may say that since I have used the improved apparatus mentioned above (7) I have had very few cases in which I could not somewhere get into the pleura. At one time I had 20 per cent. failures. Now I should put the figure at 5 per cent. or even less. I am having the records gone through.

9. I now never use nitrogen. I do not say this is a final conclusion. At one time I used nitrogen only, but I have adopted Lister's enthusiastic opinion of oxygen for the first operation and for subsequent operations. I use oxygen first and then air. The reasons for this I gave in the *Edinburgh Medical Journal*, 1915, **15**, 314.

10. The first operation is only a rehearsal to give the patient confidence and to prevent shock, and it stops short of the induction of gas. At the second operation I give 150 c.cm. of gas : at the third operation 300 c.cm. of gas: after this increase to 600 c.cm. This is an instance of my average routine. The bad effects of a larger quantity of gas can be gathered from my previous remarks.

The gas may run slowly at first and then, as it peels off one pleural surface after another, flow swiftly. I always cut off the gas bottle from the chest until I have satisfied myself that the needle-point is in the pleural cavity. I do not even open the cocks at zero level ; they are not opened until I have obtained a negative pressure, as registered in the manometer, and a respiratory oscillation. I have found aspiration by the safety syringe useful in starting a negative manometer movement. I have also found the injection of several c.cm. of air do the same thing. The value of manometric readings is comparative only. The readings vary with alteration of the patient's position.

11. (*a*) This question is very difficult to answer, every case having its own individuality. I finish an initial operation with a freely opened pleura (i. e. few or no adhesions) at a negative pressure.

Manometric levels. Saugman, in a German medical journal, says: 'One must not content oneself with small negative pressure values, two and thereabouts, unless one tries to get evidence of the position of the needle-point by use of the safety syringe.' He also says that when the needle has penetrated the chest-wall, and has not yet reached the lung, there often appears, if there are adhesions, a small negative pressure without respiratory movement, or at any rate without clear ones. I have found that when my needle has canalized a vessel the pressure in the mano-meter has become positive.

Complete compression of the lung is a condition rarely obtained and is likely to be followed by pleural effusion, which may very readily become purulent.

(*b*) I seldom collapse the lung to the extent suggested by Forlanini, Saugman, Brauer and Spengler, or Clive Riviere. I recognize that it will expand in any case between the refills unless these come very frequently. I have also been much surprised, especially since I have used a double manometer, at the ease with which I can reopen the pleural cavity even after this has completely collapsed. I am rather sceptical about these complete compressions. Gas can be introduced into the pleura in very large quantities without compression of the lung, and in early operations the gas is rapidly absorbed. I therefore do not seek or expect a constant positive pressure. I get it, however, in exceptional cases. In one of my cases the positive pressure was 15 c.cm. of water. Occasionally gas blows out of the needle with an audible result. The rule is not to have a definite pressure, which, by the by, alters according to the position, but to introduce such a pressure that the râles cease to be heard.

12. I will put it this way. I do not wish to be limited to artificial pneumo-thorax therapy. I want my patient to have the advantages of sanatorium régime, including graduated work and getting complete rest when the latter is needed. I believe also that artificial pneumothorax is valuable in most cases of advancing pulmonary tuberculosis. In incipient cases I try the usual routine treatment for a time, and I continue this treat-ment if it is doing good. In cases of dry fibrosis I never use artificial pneumothorax. In bronchiectasis I have good results from artificial pneumothorax. In one case of broncho-pneumonia coming on in a patient with a positive sputum I associated the broncho-pneumonia with the tuberculous lesion and produced an artificial pneumothorax. The effect was so magical that I was somewhat chagrined to find that the broncho-pneumonia had been a condition entirely independent of the tubercle. I thus inadvertently learnt that in one case of pneumonia artificial pneumothorax had done no harm. I do not wish to suggest to any one that they should use this treatment in pneumonia, a disease in which patients die of shock, but it has struck me that in the early stages of a unilateral case the treatment by artificial pneumothorax is open to searching criticism, but is a possible one.

In conclusion, if I were allowed but one curative agent, say artificial pneumothorax or a sanatorium, I should feel obliged, in the cases that I have described, to prefer artificial pneumothorax to the sanatorium.

V. Note on Reports by Physicians on the Value of Treatment by Artificial Pneumothorax.

1. *Number of Cases reported.*

Altogether the reports relate to between 1,400 and 1,500 cases of pulmonary disease treated by artificial pneumothorax, but, owing to certain records having been lost and others destroyed by fire, the exact number is not known. Slight reduction should also be made for the fact that the cases of Dr. Woodcock and Dr. Fernandez overlap to some extent, whilst certain of the cases

reported by Dr. Lillingston were treated in collaboration with other physicians, who, possibly, have included some of them in their own reports.

2. Indications and Contra-indications.

It is usually held, in the words of Dr. Riviere, that the ' classical' case for the induction of artificial pneumothorax is one of severe one-sided disease with the other lung clear or nearly clear to physical examination. These cases, the same authority observes, are less uncommon than might at first sight be expected, and must form a large proportion of any well-selected pneumothorax material.[1]

Difficulties naturally arise in deciding at what stage of disease the treatment is indicated and how far the extent of disease in the opposite lung, if present, is a contra-indication.

Closely bound up with this problem is the question as to how long other methods of treatment are to be essayed before recourse is had to artificial pneumothorax.

The majority of the physicians consulted are of opinion that the subjects should be selected from cases which have failed to respond to ordinary methods of treatment, such as treatment in a sanatorium, rest, hygiene, and fresh air. The cases usually selected are then those of mainly unilateral disease which have thwarted proper institutional treatment; they are doing badly, and display evidences of toxaemia and activity. The ' other' lung, if involved, should only be slightly affected. Dr. G. Lucas holds that this lung should be affected less than one-third in extent and the disease here should be inactive ; Dr. Jane Walker considers that only one lobe of this lung should be involved. Dr. Jane Walker and Dr. Esther Carling have mainly carried out the treatment in cases in which the disease in the more affected lung has usually reached an advanced stage. Whilst the above is the general expression of opinion it is not quite unanimous.

Dr. H. Morriston Davies considers that no case is too ' early' for this method of treatment. An ' early' case does not necessarily mean that the patient has got a good resistance and will therefore respond and obtain permanent or even temporary benefit by the ordinary hygienic modes of treatment. He states, therefore, that every case in which there is no definite contra-indication is a suitable one for artificial pneumothorax treatment.

Again, Dr. G. Lucas considers the treatment should be resorted to at an earlier stage of the disease than is customary at present, as too often valuable time is lost in waiting.

Dr. Woodcock and Dr. Fernandez recommend an initial period of sanatorium treatment in early cases, but if the disease in the one lung is not localized but is progressing they do not hesitate to advise artificial pneumothorax in such cases.

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[1] Vide C. Riviere, Pneumothorax Treatment of Pulmonary Tuberculosis, London, 1917, p. 12.

Dr. Riviere is of opinion that the application of pneumothorax treatment to cases of early pulmonary tuberculosis has many contra-indications. It is unnecessary since the disease can be arrested by other methods; it is inexpedient since the risks of pleural shock and pleural effusions are to be reckoned with; also the early affected lung may get bound down by adhesions and thus treatment by artificial pneumothorax at a later stage prove impossible, whereas otherwise it might have been effective. It is clear, therefore, that the ultimate decision as to the induction of an artificial pneumothorax in an early case must rest upon the experience of the physician and the circumstances of the individual case.

Cases of recurrent haemoptysis and cases of profuse bleeding from the lung which are not controllable by other means, and in which a fatal issue is to be feared, may derive benefit from an artificial pneumothorax.

Dr. Woodcock, Dr. Wingfield, and Dr. Fernandez lay stress upon the circumstance that for this treatment to be successful the disease must be mainly on one side, and the operator must ascertain not only from which lung the haemorrhage is coming, but also form an opinion as to whether the amount of 'working lung' is sufficient to 'carry on' and sustain life after artificial pneumothorax has been performed. Dr. Woodcock observes that when in doubt as to the position of the bleeding vessel, and especially if the case is a desperate one, it is wise to consider the haemorrhage as proceeding from the more diseased lung and in which the disease is more chronic, and not, as he at first considered, from the lung which shows the more recent and presumably the more acute disease.

Dr. Fernandez in his report refers to methods which he finds of value in indicating the lung from which the haemorrhage is proceeding. In cases of profuse haemoptysis, where artificial pneumothorax is performed as an emergency operation and as the only means of saving life, Dr. Riviere has stated that a large quantity of gas, 1,000 or 1,500 c.cm., may be put in at once, the needs of the moment outweighing the usual contra-indications. In ordinary cases of recurrent haemoptysis such large quantities are not necessarily required to arrest the bleeding. Masenti, Borgogno, and Vergano in their five cases found that no great amount of collapse was needed, nor even a positive intra-pleural pressure to achieve this object. A quantity of gas varying between 250 c.cm. and 1,100 c.cm. proved sufficient.

Dr. Morriston Davies considers the following are special indications for the treatment: haemorrhage; cavities; pneumonic tubercle; tuberculosis of the lung and larynx; pulmonary tuberculosis in young adults; pulmonary tuberculosis in those who have to return to an unsuitable environment; pulmonary tuberculosis in those who have to mix with fellow workers indoors; pulmonary tuberculosis in those whose work is connected with foods; pulmonary tuberculosis in mothers with young children; when other means have been tried and have not proved successful, or when the disease recurs after arrest.

Dr. Woodcock and Dr. Fernandez also consider that the indications for this treatment might be extended with advantage, and their reports should be specially consulted on this question. It will be noted that they advocate the treatment not only for selected cases of chronic pulmonary tuberculosis and chronic discharging sinus following on a tuberculous empyema, but, in addition, for certain pulmonary cases of a non-tuberculous character, such as bronchiectasis, abscess, and gangrene of the lung, and possibly cases of unilateral lobar pneumonia. On the evidence submitted, it would seem desirable that further investigations should be carried out as to the efficacy of the method in such cases of non-tuberculous pulmonary disease.

Laryngeal tuberculosis *per se* is not to be regarded as a contra-indication for treatment. Dr. Lillingston points out that active laryngeal tuberculosis often clears promptly when the pulmonary disease is arrested by an artificial pneumothorax. Da Gradi and Zink have recorded similar favourable results. As regards the special contra-indications for induction of artificial pneumothorax these are succinctly grouped by Dr. H. Morriston Davies as follows :

1. Extensive disease on the opposite lung. At least two-thirds of the opposite lung should be healthy.
2. Tuberculous enteritis.
3. Tuberculous glands or extensive disease elsewhere (except in the larynx).
4. Renal or cardiac inadequacy or disease.
5. Elderly people who show a reasonable power of resistance.
6. Generalized bronchitis, asthma.
7. Bilateral secondary infection.
8. People highly strung or of an extremely nervous disposition.

With the addition of diabetes these are special contra-indications that receive general acceptance. The majority of the physicians would, as previously remarked, exclude cases of early pulmonary tuberculosis reacting well to sanatorium treatment. Dr. Lillingston maintains that it is not so much the extent of involvement of the opposite lung as the activity of the disease therein that should rule out artificial pneumothorax. He states that active disease in both lungs is a contra-indication, but extensive and inactive disease in the better lung is no bar to treatment. Other contra-indications cited by Dr. Lillingston are moribund cachectic cases, age over sixty years, mental instability, and bilateral renal tuberculosis.

Dr. Woodcock and Dr. Fernandez in their reports give a careful analysis of the contra-indications which they find of importance in their experience.

The question of pleural adhesions as contra-indicating artificial pneumothorax is subsequently considered.

3. *Effect of a Pneumothorax upon the Functioning Lung.*

When the diseased lung is compressed by an artificial pneumothorax the healthier lung has to be responsible for the whole function of respiration. If this lung is undiseased little difficulty

will be experienced, and even if a small amount of disease is present one would anticipate that the respiratory function would be maintained with more or less success. It is a common experience in the post-mortem room of Brompton Hospital to see lungs with extensive bilateral tuberculosis which belonged to patients who experienced little dyspnoea or general respiratory distress during life, although the area of unaffected functioning lung tissue in such cases must have been extremely small.

In Dr. Morriston Davies's experience no evidence appeared that emphysematous or other changes occur in the opposite lung, if healthy, after the induction of an artificial pneumothorax. Dr. Sutherland, however, has found a certain amount of compensatory emphysema, and considers that the breath-sounds in the unaffected lung approximate to a more puerile type. Dr. Rolleston is of opinion that the opposite lung is unaffected provided there is no dislocation of the mediastinum. Dr. Woodcock considers that the healthy lung is protected by the treatment as the risk of infection from the actively diseased lung is minimized. Dr. Fernandez considers that the maintenance of intra-pleural pressure within a negative limit safeguards the functioning lung from harm. In his first inductions of large dosage he apprehended that as a result one or two unilateral cases of pulmonary tuberculosis developed bilateral disease subsequently. Dr. Wingfield and others report no evil effects upon the sound lung save an occasional pleurisy over the lower lobe.

We may now consider the effect of an artificial pneumothorax upon the opposite lung when this lung is diseased. Dr. Carling's experience is unfavourable in a certain proportion of cases, but the subjects suffered from advanced pulmonary tuberculosis. Dr. Riviere considers that quiet and localized disease generally improves, but otherwise the effect of a pneumothorax is harmful. Dr. Felkin finds the effect of the treatment generally beneficial except in a few ' desperate cases' where the activity of the disease in the better lung was increased. Dr. Morriston Davies states that when the disease is a definite localized peribronchial lesion, collapse of the ' one lung' has almost always a beneficial effect upon the ' other lung'. When, however, the distribution of the disease in the ' other lung' is such that the indications suggesting that the disease is merely a spread from the ' one lung' are absent, improvement may or may not take place. It depends then on the general resistance of the patient, and on whether the control of the disease in the ' one lung' will allow of a sufficient increase in the ' health resistance' to enable the patient himself to deal with the disease in the ' other lung'.

Dr. Lucas considers that when one tuberculous lung is extensively involved and the other slightly so, a considerable amount of compensatory emphysema takes place in the ' sound' lung. Now when an artificial pneumothorax is produced, the emphysematous lung is subjected to pressure, and consequently compression is brought to bear on the vessels and some obstruction to the circulation in that lung is produced. This in turn pro-

duces venous stasis. Thus there is produced in the 'sound' lung the essentials aimed at in Bier's treatment of tuberculosis by passive hyperaemia, a condition of the lung which tends to bring about arrest rather than excitation of the disease.[1]

Dr. Woodcock finds that usually a pneumothorax which lessens the daily amount of purulent sputum benefits both lungs, pulmonary tuberculosis being almost invariably bilateral. Summing up the evidence it would appear that in both cases of unilateral disease and cases of bilateral disease with a localized inactive lesion in the functioning lung, no harmful, but rather a beneficial, effect is exercised upon the 'opposite' lung by the induction of an artificial pneumothorax. In cases where the disease in the functioning lung is active and unlocalized the operation seems fraught with risk, as the disease may spread rapidly in this lung.

The risk of 'lighting up' a localized quiescent lesion in the functioning lung is one which must be taken into consideration when deciding on the advisability of artificial pneumothorax, but which fortunately seems to be negligible as a rule.

4. *Induction of Artificial Pneumothorax on both sides in the same Patient at different times.*

In cases of pulmonary tuberculosis affecting both lungs, partial and, if necessary, simultaneous bilateral collapse is advocated by Dr. Parry Morgan, to whose published paper reference should be made. Dr. Tattersall tried the method in one case, but only temporary improvement was obtained; Dr. Walker has seen the method carried out in Italy. The question we propounded was whether an artificial pneumothorax had been induced in the same patient at different times. Only five physicians record personal experience of this method.

Dr. Lucas has attempted a double compression in one case. The second compression failed owing to the presence of pleural adhesions. He believes this form of treatment in certain cases to be sound. Dr. Morriston Davies has carried it out in three cases. Dr. Fernandez has performed bilateral compression at different times in 11 cases; of these, 3 are still alive; 4 are doing well; 1, in whom pyrexia was controlled by the treatment, is not doing well, and the prognosis is bad; 3 are dead. He observes that bilateral induction needs careful selection, and that the dosage of gas should be small; high pressures are to be avoided.

Dr. Woodcock does not give the number of cases treated, but states that he has performed the double operation often; he had four advanced cases under treatment at the time of report. Dr. Tattersall essayed the double operation in one case. The originally affected lung again expanded and the disease in it became active. No benefit was obtained. On the whole, the results of bilateral compression are not favourable.

[1] See, however, Chapter X. p. 48. of Dr. L. S. T. Burrell's Report. Part I.

5. *Accidents and Complications in the Treatment.*

A. *Pleural Effusion.* This is the commonest complication of treatment. Dr. Carling records that in 17 of her cases pleural effusion stopped further treatment. In her experience it is usually a fairly late complication, but it may occur at any time. In 5 out of 19 cases Dr. Felkin found a clear serous effusion in 3 cases, and in 2 cases a purulent effusion. Dr. Lillingston found that one-third of the cases treated developed a pleural effusion. Dr. Lucas notes that pleural effusions usually occur between the third and sixth month of treatment. Dr. Riviere considers that the pleurisies encountered in the course of artificial pneumothorax treatment are usually harmless. Dr. Rolleston records pleurisy in well over 50 per cent. of his cases, Dr. Tattersall in 38 per cent., and Dr. Sutherland found a simple pleural effusion in 2 cases. For the six cases of pleural effusion arising in the course of the treatment described by Dr. H. Morriston Davies reference should be made to his report. As regards precautions and treatment of the condition, Dr. Woodcock is of opinion that acute pleurisy is more likely to occur after a small injection of gas than after a large injection. He favours the giving of morphia as likely to abort an attack of pleurisy. Dr. Fernandez has successfully treated the complication of pleural effusion by aspiration and replacement with oxygen. Dr. Carling has found it more satisfactory not to aspirate, but to allow the liquid to keep up the compression. Dr. Morriston Davies urges that the liquid should always be removed because of (1) its effect on the patient, producing as it does a decided feeling of malaise and possibly chronic fever, (2) the tendency of adhesions to form or the lung to become incapable of re-expansion owing to the thickening of the visceral pleura, (3) the risk of secondary infection. Unless the liquid subsides rapidly and shows no tendency to recur, it should be removed and the liquid and part of the gas in the pleural cavity replaced by oxygen and, when the liquid has ceased to recur, the pneumothorax maintained by nitrogen.

B. *Subcutaneous or Surgical Emphysema.* (a) *Superficial Emphysema* (see Dr. Woodcock's report). Dr. Lillingston, Dr. Lucas, and Dr. Rolleston record instances of this complication.

(b) *Deep Emphysema.* Dr. Woodcock considers this a dangerous complication which may even cause the death of the patient. His report should be specially consulted on this complication.

C. *Reactions.* Dr. Morriston Davies calls attention to the following reactions which may ensue on treatment:

1. Pure tubercular reaction.
2. Coli or streptococcal toxaemia reactions.
3. Mixed reaction.

The last two reactions are the most serious and are due to toxaemia from the intestinal tract as the result of intestinal stasis. The causal organism is generally *Bacillus coli*, and in these cases sulphur-ethers will be found in the urine in large quantity and, usually when nausea is a symptom, acetone as well. If such reactions occur they may be so prolonged in those cases

in which the cause is not recognized and treated, that the artificial pneumothorax has to be abandoned.

Dr. Morriston Davies advises the following precautions and treatment of these reactions. Routine and constant testing of the urine for sulphur-ethers; in patients suffering from chronic intestinal stasis the giving of calomel or castor oil before an injection of gas.

Streptococcal cases are treated by vaccines, whilst the pure tubercular reactions are controlled by the amount of gas introduced.

D. *Pleural Shock or Pleural Reflex.* Dr. Carling records three cases of pleural shock, all of whom recovered. Dr. Lillingston has had one case of pleural reflex; it occurred twice in the same patient and was not fatal. Dr. Pearson has seen one death within an hour of the initial injection which was ascribed to pleural reflex. In one case treated by Dr. Wingfield sudden loss of consciousness occurred with subsequent death due, presumably, to pleural shock. Dr. Woodcock reports that of the complications seen, shock has been most common. He avoids this by undertaking a ' preliminary operation ' in which he goes through all the steps of the operation without actually introducing gas. This method allays the psychic factor in pleural shock. Pain is another factor, and this can be minimized by local anaesthesia and by giving morphia after the operation, if the pain is severe. Dr. Woodcock finds that morphia given before the operation may increase shock, the patient having been alarmed by nausea. In Dr. Lillingston's patient, after signs of pleural reflex had occurred at two refills, both hypodermic injections of morphine and local anaesthesia were prescribed at every refill, and no further signs of pleural reflex occurred. Dr. Lucas writes:

' Warming of the nitrogen before introducing it into the pleural sac has, in my opinion, the effect of causing less shock and diminishing subsequent discomfort by avoiding to a considerable extent the subsequent expansion of the gas, which, if introduced cold, is warmed up to the body temperature.'

For the treatment of pleural shock Dr. Woodcock advises artificial respiration, massage of the heart by pressing the diaphragm up, pushing the fingers under the ribs, administering oxygen by a tube through the nostrils and the giving of pituitary extract, the object being to overcome sudden ventricular dilatation.

E. *Gas Embolism.* No definite cases of this complication are reported, but Dr. Woodcock and Dr. Fernandez note one slight case of hemiparesis which might have been an embolism from gas or from a small amount of solid débris. Dr. Woodcock describes in detail precautions which he has found to be of value in avoiding gas embolism.

F. *Natural Pneumothorax occurring after Artificial Compression.* Natural pneumothorax may occur either in the functioning or in the compressed lung. Dr. Carling records two cases of this condition. In one a natural pneumothorax developed on the untreated side after violent coughing; death ensued within a

week. The other patient had resumed full work as a chauffeur. While winding up a heavy car he felt sudden pain and a sense of 'something giving way'. Hydropneumothorax developed, and eventually death took place.

Dr. Morriston Davies reports that on two occasions a comparatively slight spontaneous pneumothorax has occurred within two days of a refill on the same side as the artificial pneumothorax. In both cases the lung was in part adherent, but no bands of adhesions could be seen by the X-rays, and a small positive pressure only had been left. The increase in pressure in neither case was sufficient to necessitate active interference.

In one of Dr. Lillingston's cases rupture of a pyopneumothorax into the lung took place with a fatal issue. Dr. Riviere notes one case of perforation of the lung. Dr. Tattersall reports that rupture of the lung occurred in one case, causing a spontaneous pneumothorax and great dyspnoea. The pressure was relieved three times by aspirating air, and although a pleural effusion developed, this did not become purulent; the ultimate result was good.

G. *Haemoptysis due to Puncture of Lung.* Dr. Wingfield records one instance of this complication.

H. *Infection of the Track of the Needle.* This condition has been seen by Dr. Morriston Davies in cases sent to him. As he observes, it should not occur if proper aseptic precautions are taken.

I. *Displacement or Dislocation of the Mediastinum.* Reference is made to this complication by Dr. Rolleston and Dr. Morriston Davies. Dr. Rolleston is of opinion that it can be avoided by using low pressures of gas, and, as Dr. Morriston Davies notes, it should never occur to an extent to cause serious complications if the treatment is properly controlled by the X-rays.

J. *Bulging of the Right Vertebro-Mediastinal Pleural Sinus.* Two cases of this complication are recorded by Dr. Morriston Davies.

On the whole, a study of the physicians' reports makes it clear that apart from pleurisies and pleural effusions which are exceedingly common, the accidents and complications of the induction of artificial pneumothorax, in expert hands, are either extremely rare or may be avoided by taking special precautions. Perhaps pleural shock or reflex must at present be regarded as an exception to this general statement. Although not of common occurrence it occasionally appears even when the treatment is in the hands of an operator with extensive experience who has taken all due precautions against the condition. It is certainly a possible risk which should be placed before the patient and his friends before their consent is given to the induction of an artificial pneumothorax.

6. *Results in Cases with Pleural Adhesions.*

The physicians consulted express different opinions as to the value of an artificial pneumothorax in cases of pulmonary disease with pleural adhesions. The experience in this respect of

Dr. Walker, Dr. Carling, Dr. Rolleston, and Dr. Wingfield has been unfavourable. Dr. Pearson gives a similar opinion except in cases where the adhesions are only partial and an effective pneumothorax can be produced compressing the lung where the most active disease is present. Of 64 patients treated by him during ten and a half years, 21 had partial but effective—or temporarily effective—compression produced, while in the remainder (43) the compression was complete. As Dr. Sutherland observes, the results are not good if adhesions prevent collapse to a material extent. Dr. Lillingston considers the results are only satisfactory in cases with strictly limited adhesions, notably adhesions confined to the apex of the lung. Dr. Lucas writes: 'If I find only a small loculus, it has not been my practice to break down adhesions by forcible pressure. But in one case in which I found a small pleural space very material benefit accrued to one patient by keeping this comparatively small loculus filled.'

On the other hand, several physicians have found great benefit result from artificial pneumothorax in cases with adhesions. Dr. Morriston Davies, Dr. Felkin, Dr. Blanford, Dr. Riviere, Dr. Tattersall, Dr. Fernandez, and Dr. Woodcock all report favourable results, even although only incomplete collapse may have been obtained in a certain proportion of cases.

Dr. Morriston Davies considers the treatment may be attempted with success provided that a collapse equal to half the lung can be obtained. When the adhesions are such as to allow of it, he stretches them by maintaining a fairly constant pressure on the lung; when this is dangerous owing to the condition of the lung at the point of attachment of the adhesion, or stretching is impossible, he divides the adhesion if division is practicable.

Dr. Woodcock notes that most of his operations have been in the presence of adhesions.

7. *Observations on the Technique and Apparatus; the Employment of Local Anaesthesia.*

All the physicians agree that the technique should be that of a surgical operation, strict asepsis being maintained, and that the apparatus should be as simple and portable as possible.

Dr. Morriston Davies in his report gives a useful list of essential points regarding the apparatus. Certain of the physicians have designed forms of apparatus or have introduced valuable modifications and appliances in operative procedure. These standard forms of apparatus are well known and need not be recapitulated here. Valuable observations as to technique and apparatus are given in the several reports.

With regard to local anaesthesia opinion is unanimous as to its value in the initial operation, and, in view of the risk of pleural shock, many recommend its use at all subsequent refills. 2 per cent. novocain appears to be generally used.

8. *Failure to produce a Pneumothorax.*

The percentages of failure to produce a pneumothorax vary with the class of case treated. The usual figure given for failure ranges from about 10 to 20 per cent. of cases.

Experience and improvement in the technique and apparatus, together with more knowledge as to the selection of cases, undoubtedly minimizes the percentages of failure.

9. *The Choice of Gas.*

The selection of the most suitable form of gas is made from nitrogen, oxygen, or air.

(a) *Nitrogen.* Nitrogen is employed by Dr. Morriston Davies, Dr. Felkin, Dr. Lucas, Dr. Pearson, and Dr. Sutherland.

(b) *Oxygen.* This is preferred for the initial operation by Dr. Carling, who employs nitrogen or filtered air for refills. Dr. Woodcock uses oxygen for the initial operation and then air. He formerly employed nitrogen. Dr. Wingfield formerly used oxygen initially and nitrogen for refills, but for the past three to four years he has used air and finds it equally efficacious. Dr. Fernandez alone uses oxygen invariably throughout the treatment. He quotes Dr. Benjamin Moore's opinion as to the inhibiting effect of oxygen upon the tubercle bacillus. In his view the supposed lessened absorption of nitrogen, even if true, is not an advantage so long as total collapse of the lung is not aimed at. He believes that nitrogen users have more cases of pleural effusion than occurs in his practice.

(c) *Air.* Dr. Blanford, Dr. Lillingston, Dr. Walker, and Dr. Wingfield use air ; Dr. Walker formerly employed nitrogen. Dr. Riviere, Dr. Carling, Dr. Sutherland, and Dr. Tattersall consider nitrogen and air are equally efficient. Helium and carbon dioxide have also been used (see Part I, Chapter I, p. 12).

Dr. Rolleston considers the choice of gas unimportant.

The chief claim for the use of oxygen at an initial operation is that oxygen being more readily absorbed by blood the risk of gas embolism is minimized. Dr. Riviere has pointed out that this reasoning would only apply to the wounding of veins in the thoracic wall and not to the pulmonary veins containing arterial blood, which, as Brauer states, have no special power of absorbing oxygen. Dr. Lillingston observes in his report that the use of oxygen may give a false sense of security to the operator. The use of oxygen throughout the treatment, as advocated by Dr. Fernandez for the reasons given above, implies that partial collapse of the lung only is desired as this gas is so readily diffusible, and, for the same reason, the employment of oxygen entails the giving of frequent refills, which is not always convenient to the patient. In the opinion of most authorities therefore the choice rests between nitrogen and atmospheric air. As the evidence cited shows, several physicians who previously employed nitrogen have discarded this gas in favour of air as being in their experience equally efficient, more readily available

and less costly. It is true that nitrogen is less diffusible than air and consequently is decidedly preferred by certain physicians. The remarks of Dr. Felkin and Dr. Morriston Davies on the advantages of employing nitrogen should be duly considered in this connexion.

10. *The Amount of Gas desirable at the Initial Operation; Bad Effects observed after the Administration of a large quantity of Gas.*

The physicians' opinion is unanimous that the initial volume of gas should be small in amount, the pressure being maintained and augmented by frequent refills. The usual quantity advised is about 300 c.cm. Saugman has stated that this amount should never be exceeded at the first operation and recommends 200–250 c.cm. Dr. Riviere, however, sometimes gives 400 c.cm. where the succeeding interval has to be as long as four days and where this amount of gas disturbs the pressure but little, and he has never seen any ill effects from it. Dr. Lucas gives 500 c.cm. initially, and from 400 to 600 c.cm. is the range advised by Dr. Felkin, although, as a rule, he did not exceed 500 c.cm. Dr. Morriston Davies rarely gives more than 200 c.cm. at the first essay ; Dr. Sutherland and Dr. Woodcock about 150 c.cm.

Dr. Wingfield considers the amount of gas administered unimportant, but directs special attention to the change of intra-thoracic pressure ; the pressure should not be altered by more than 2–3 cms. of water until complete collapse or sufficient collapse has been obtained.

The administration of large quantities of gas is generally deprecated except in cases of haemoptysis, when, in order to ensure an immediate partial collapse of the lung, a large quantity of gas, 1,000 c.cm. or more, must needs be run in without delay (Riviere). In the ordinary case for which artificial pneumothorax is induced, Dr. Riviere advises the putting in of 500–800 c.cm. at each filling after the first, perhaps some 500 c.cm. at the second filling, and 500–800 c.cm. at the third, fourth, and fifth fillings. He adds, ' It has been calculated that the adult pleural cavity holds some 2,000–3,000 c.cm. of gas, but an unknown allowance must be made in each case for re-absorption during the intervals between the refills '.

Dr. Carling considers that the quantity of gas should never exceed 1,000 or 1,100 c.cm.

Here again, however, the reports of Dr. Lillingston, Dr. Lucas, and Dr. Carling in particular confirm Dr. Wingfield's observation that ill effects arising after a large quantity of gas are dependent more on the intra-pleural pressures produced than on the actual quantity of gas injected. The bad effects recorded are usually dyspnoea, pain, acceleration of the pulse-rate, anxiety, sweating; Dr. Morriston Davies has seen severe ' reactions ' after large doses; and Dr. Rolleston notes pain and, if a large amount of gas is persisted in, dislocation of the mediastinum with great dyspnoea. From these reports, the desirability of admitting a small initial

dose of gas with the maintenance of pressure on the lung by small and frequent refills, little change being made in the intra-thoracic pressure, appears to be fully established.

11. *The Pressures obtained (a) after the Initial Operation, (b) when the Lung has been well collapsed.*

In replying to this question many of the physicians pointed out that the pressures obtained varied with the individual case, and that it was impossible to prescribe any general rule in either circumstance. This is obviously the case, but the information given enables one to say that the practice is to leave a negative pressure after the initial operation. This assumes, however, that the pleural cavity is free of all adhesions. In this event, as Dr. Morriston Davies states, the pressure obtained at the end of the initial operation will certainly be negative, but the inspiratory pressure may vary from one equal to -9 mm. of mercury whilst the expiratory may vary from -6 to -2 mm. of mercury.

When adhesions are present, the pressure at the end of the initial operation may be negative or positive.

When there is an exudate of lymph between the two surfaces, the expiratory pressure will be positive, but the inspiratory pressure will be either negative or positive. At subsequent injections both may become negative.

Several physicians prefer to maintain a negative pressure for the early injections of gas. Dr. Lillingston remarks that such a pressure indicates comparative freedom from adhesions.

Later, when the lung is well collapsed, the pressure at the end of an injection should be determined by the needs of each case. Reference may be made to the individual reports for an account of the terminal figures of pressure that are usually obtained, subject to the above proviso.

Dr. Fernandez and Dr. Woodcock express doubts as to the value of complete compression of the lung. In Dr. Woodcock's experience complete compression of the lung is rarely obtained, and, when obtained, is likely to be followed by pleural effusion which may readily become purulent. The treatment by these physicians then is not directed towards complete compression, and a negative pressure is often maintained throughout and at the termination of the course. Dr. Fernandez notes that in cases that have done well after two to three years a negative pressure is still maintained.

All authorities agree that high pressures are to be avoided. In the absence of clinical data we have not attempted to discuss here the value of the bilateral partial compressions advocated by Dr. Parry Morgan. Dr. Parry Morgan himself writes: 'My experience, therefore, although it proves the practicability of inducing a moderate degree of pneumothorax bilaterally and leaves me hopeful regarding the utility of partial collapse, is too limited to justify me in attempting to give a definite estimate of its value, and I would do no more than commend it for consideration.'

12. *Conclusion.*

The final question asked of the physicians was: 'What is your opinion as to the value of the treatment?' As our review of their reports has already intimated a favourable answer is returned by all with no uncertain voice. The induction of artificial pneumothorax in pulmonary disease and especially in selected cases of chronic pulmonary tuberculosis is a great advance in therapy. Many cases of pulmonary tuberculosis which proved intractable to ordinary hygienic treatment have undergone complete arrest and are now enjoying good health as the result of the method; others, and principally those treated by this method in whom the disease was in an advanced stage when the treatment was initiated, have had their lives ameliorated and considerably prolonged. Statistical evidence supporting this statement is given in Chapter XII of Dr. L. S. T. Burrell's Report (Part I).

From the reports opinion seems unanimous that for selected cases of pulmonary tuberculosis this is the most valuable form of treatment we possess.

Where difference of opinion prevails to a slight extent is in the selection of the case of pulmonary tuberculosis for treatment. The physician may hesitate between the Scylla of treating too early a case and the Charybdis of being faced with a case too advanced for operation. The indications and contra-indications for artificial pneumothorax as laid down in the reports have already been fully discussed, and we can only say here that, however doubtful the operator feels of employing the method for an early case of tuberculosis, as soon as he perceives the disease is not yielding to ordinary methods of treatment, an artificial pneumothorax should be induced as soon as possible. In carrying out this procedure he will find all authorities agree that he will be giving his patient the best possible chance of recovery.

For the arguments against the treatment of early cases by the method Dr. Riviere's book, *Pneumothorax Treatment of Pulmonary Tuberculosis,* may be specially consulted, while reference may be made to Dr. Morriston Davies's report for advocacy of the employment of artificial pneumothorax in a larger proportion of early cases than has hitherto been customary.

It should be observed that several of the reports of the physicians lay stress upon selection of the case and control of pneumothorax treatment by means of the X-rays.

In conclusion, we express the hope that the presentation and publication of these reports written by physicians who have devoted their attention to the efficacy and problems of artificial pneumothorax, may not only enhance scientific knowledge of the subject but also lead to a more general adoption of this valuable method in the treatment of pulmonary disease.

L. S. T. Burrell.
A. Salusbury MacNalty.

PLATE II

PLATE I

PLATE IV

PLATE III

PLATE VI

PLATE V

PLATE VIII

PLATE VII

PLATE X

PLATE IX

PLATE XII

PLATE XI

Ray

PLATE XIV
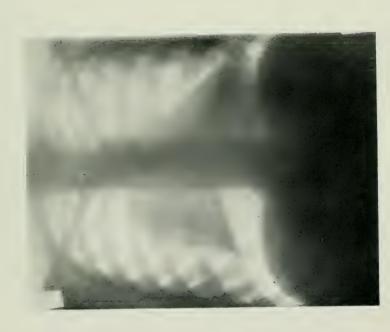
PLATE XIII

PLATE XVI

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PLATE XVII

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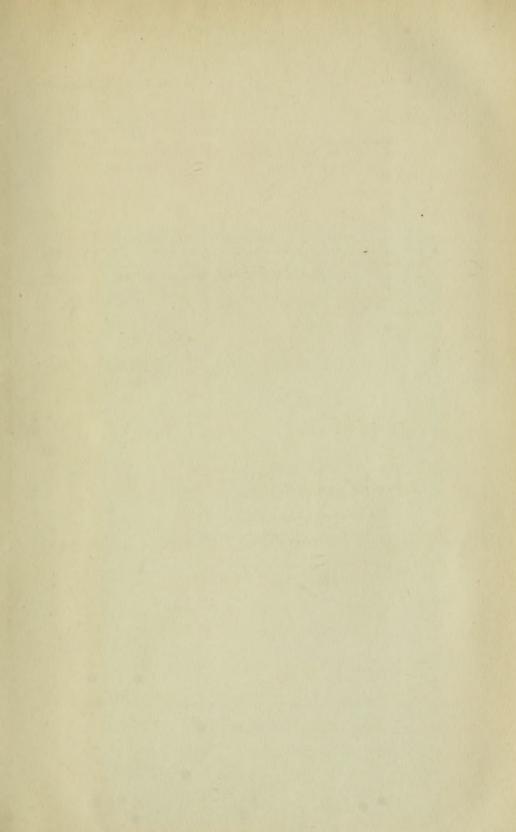
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